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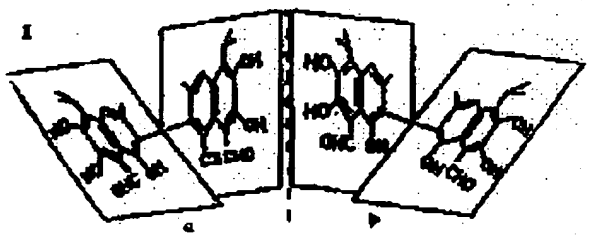
[54] Name of Invention: A Method for the Preparation of Optically Active Gossypol

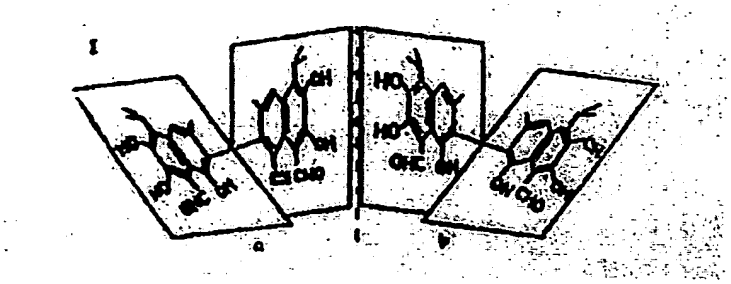
[57] Abstract

A method for the preparation of optically active gossypol of the formula Ia/Ib. This method includes: a) (i) hydrolyzing a (+) or (-) gossypol with an optically active amine, and, (ii) when necessary, purifying the (+) or (-) gossypol obtained, or, b) removing the lower quantity type from two unequal quantities of (+) or (-) gossypol antipode and obtaining the other type of antipode.



Claims

1. A method for the preparation of optically active gossypol of formula 1a or 1b at a high production rate.



Said method includes:

a) A mixture of a (+) gossypol and a (-) gossypol and an optically active amine bonded to obtain a (+) gossypol and a (-) gossypol optically active amine compound;

b) The product of a) is hydrolyzed in a solvent in the presence of a catalyst;

c) The product of b) is treated by chromatography or crystallization method and a (+) gossypol or a (-) gossypol is obtained; or

d) The product of a) is converted under catalysis to a diasteromer mixture with (+) gossypol and (-) gossypol at better balanced ratio;

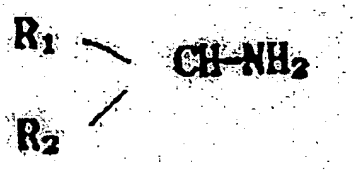
e) Steps b) and c) are repeated and a (+) gossypol or a (-) gossypol is obtained; or

f) The hydrolysate in b) is treated with formic acid or acetic acid in a solvent with a precipitate of (+) gossypol and (-) gossypol being obtained;

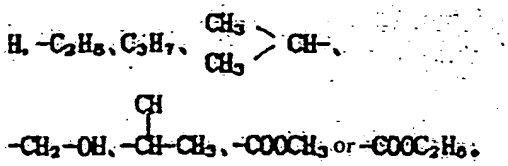
g) The precipitate is removed by filtration;

h) The filtrate is treated with an alkali, after which extraction is performed and (+) gossypol or (-) gossypol is obtained.

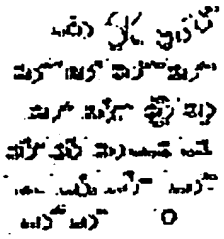
2. A method as described in Claim 1 in which the optically active amine in a) is represented by the following formula:



Wherein, R_1 represents



R_2 represents



3. A method as described in Claim 1 in which the catalyst in b) is selected from concentrated or diluted hydrochloric acid, hydrochloric acid-acetic acid, sulfuric acid, -methylbenzene sulfonic acid and cationic exchange resin or mixtures thereof.

4. A method as described in Claim 1 in which the chromatographic method described in c) indicates normal pressure liquid chromatography, medium pressure liquid chromatography and high pressure liquid chromatography.

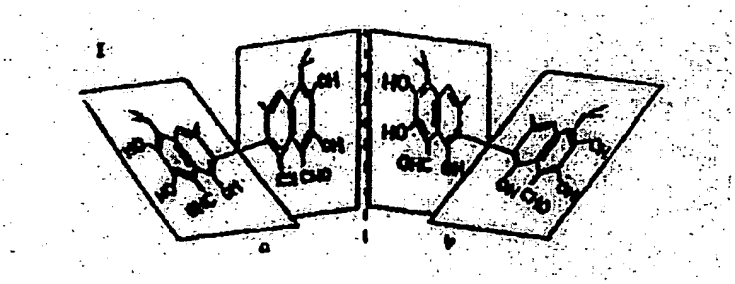
5. A method as described in Claim 1 in which the crystallization method described in c) indicates the re-crystallization method or the chromatographic crystallization method.

6. A method as described in Claim 1 in which the catalysis described in d) indicates photo catalysis or free group promoter catalysis.

7. A method as described in Claim 6 in which 2,2'-azobis-2-methylpropionic [illegible] is used as the free radical promoter.

8. A method as described in Claim 1 in which the solvent that is used is selected from Diethyl ether , acetone, chloroform, dichloromethane, and benzene or mixtures thereof.

This invention relates to a method for preparing optically active gossypol; of formula 1a/b.



Gossypol is a polyphenolhydroxybis naphthaldehyde compound that is present in the seeds, roots and stalks of Upland Cotton and Gossypium, both are Malvaceae plants. Racemic gossypol has been used in more than [illegible],300 clinical cases and it has been demonstrated that it has an antifertility action in

males (National coordination group in male contraception, Chinese Journal of Medicine, 58 (1978), 455), with an efficacy rate of 99.96%. Some users developed symptoms of hyperkalemia during its trial use (the patients exhibiting loss of strength and "weakness" to the point of paralysis and it is thought that this is the principal obstacle to the clinical use of racemic gossypol. In 1979, the Shanghai Pharmaceutics Institute of the Chinese Academy of Sciences extracted (+) gossypol from the leaves of natural plants T.populnea (L.)Soland and used it in animal experiments, demonstrating that it differed from racemic gossypol, demonstrating that it did not have an antifertility action (Wang Yuee et. al, Pharmaceutical Journal, 14 (1979), 662). From this, they concluded that (-) gossypol was the antifertility optically active isomer. This discovery aroused the interest of research workers in (-) gossypol and the World Health Organization also funded several labs in extracting (-) gossypol in natural plants and in research on analyzing racemic gossypol, further promoting research on the antifertility action and other biological activities of (-) gossypol and stimulating the use of gossypol, the synthesis of its derivatives and the development of theoretical research, and, in particular, research on the antifertility activity and toxic action of optically active gossypol. This was of major importance and deep significance in the use of pharmacological methods of high safety in controlling population growth.

Optically active gossypol can be extracted from natural plants or can be obtained by breaking down racemic gossypol. Up to 1987, no natural plant resource had been discovered for directly obtaining (-) gossypol using extraction method. In 1971, Dechary et al. (Dechary, J.M. and Pradel, P.J., Am Oil Chem. Soc. 48 (1971) 563) attempted to break down racemic gossypol in two ways. The first was using optically active biological alkalis such as, morphine, quinine and cinchonine to treat the gossypol based on the acidity of the phenol groups of gossypol, in the hope that breakdown could be achieved by salt formation. The second was to use a method in which the aldehyde groups in the gossypol molecule and an optically active [illegible] such as (s)=1=methyl phenylacetic acid, R-naphthylacetic acid and (s)-2-chloro-1-propioni acid are bonded. However, the desired results were not obtained in any of the cases. The authors were not able to explain the cause. In addition, specific experiments were not presented. Subsequently, several laboratories carried out research in this field. Success was first achieved in breaking down gossypol to (+) and (-) optically active gossypol (Si Yikang, et al., Scientific Bulletin, 28 (1983), 10: 640]. However, because the method was complex and quantity prepared was small, the method was not suited to providing gossypol in large quantities. Subsequently, Matlin et al. in [illegible] reported using HPLC method to break down racemic gossypol [Matlin, S.A., et al., J. of High Resolution Chromatography and Chromatography Communications 7 (1934), 629]. However, because the method uses expensive materials and the conditions are not easily controlled, it is not suited to use in industrial practice.

The objective of this invention lies in developing a new method for the preparation of optically active gossypol of practical value using simple procedures and convenient materials.

The methods of preparing optically active gossypol described in this invention can be divided into three methods, which are as follows. I. A method of preparing optically active gossypol by breaking down racemic gossypol or a mixture containing unequal amounts of (+) and (-) gossypol. II. A method in which (+) and (-) optically active gossypol is converted to a diastereomer and hydrolyzed, with any one type of optically active gossypol being obtained to the greatest possible extent. III. A method in which a mixture of antipodes containing unequal amounts of (+) gossypol and (-) gossypol antipode is treated with an acid that can form a 1 : 1 composite precipitate with racemic gossypol, in which one of the antipodes of a lesser quantity is removed by the precipitation method and the other antipode of a high degree of optical purity and of a higher content is obtained.

This invention therefore provides a process of technology involving a simple procedure that can be used in industrial production and that has economic value.

Specifically speaking, this invention provides

I a method of preparation of optically active gossypol from racemic gossypols Ia/b or unequal amounts of (+) and (-) gossypol. This method includes the following steps:

a) The racemic gossypol or a mixture containing unequal amounts of (+) and (-) gossypol is subjected to a bonding reaction with an optically active primary amine of the monoamine type;

b) The diastereomer of reduced optical activity of the racemic gossypol obtained or the diastereomers

of the optically active amine containing unequal amounts of (+) and (-) gossypol are separated by chromatography or the crystallization method, with an optically active amine of (+) gossypol and an optically active amine of (-) gossypol being obtained;

c) The optically active amine of (+) gossypol and the optically active amine of (-) gossypol that are obtained are hydrolyzed separately in a solvent and in the presence of a catalyst, with (+) gossypol or (-) gossypol being obtained; and

d) If necessary, the recrystallization method is used to further increase the chemical purity and the optical purity of the (+) gossypol or (-) gossypol.

II. A method in which (+) and (-) gossypol is [illegible] with a diastereomer of an optically active amine converted and hydrolyzed and an optically active gossypol of any required type is prepared to the maximum extent. This method includes the following steps.

a) (i) One isomer of the aforementioned two diastereomers is partially converted to another type of isomer in a solvent and under catalytic conditions, with a mixture being obtained that contains the aforementioned two types of diastereomers;

or

(ii) The diastereomer component of higher content in the mixture of the aforementioned two diastereomers of different content is converted to another type of diastereomer, making the ratio of the two types of diastereomers obtained closer to an equilibrium mixture of the diastereomers;

b) The mixture of diastereomers obtained is treated by chromatography or the crystallization method in order to separate the desired diastereomer.

c) The diastereomer that is obtained is hydrolyzed in a solvent and in the presence of a catalyst, with (+) gossypol and (-) gossypol being obtained.

d) If necessary, the recrystallization method is used to further increase the chemical purity and the optical purity of the (+) gossypol or (-) gossypol.

III. A method in which gossypol of a higher content is extracted from a mixture containing unequal amounts of (+) and (-) gossypol using the acid precipitation method. This method includes the following steps.

a) An acid that can produce a 1 : 1 composite precipitate with equal amounts of (+) gossypol and (-) gossypol is added to a solution containing a mixture of unequal amounts of (+) and (-) gossypol and the composite that is formed is separated and removed by the precipitation method, leaving as a residue the gossypol of higher content with its type of optical activity.

b) Extraction is performed using an organic solvent and the optically active gossypol and acid in the mother liquor are separated by neutralization in alkali.

c) If necessary, the recrystallization method is used to further increase the chemical purity and the optical purity of the optically active gossypol that is obtained.

The equipment and reagents that is required for providing the aforementioned three methods of this

invention is all essential products of the chemical industry and the pharmaceutical industry, the procedure and methods are simple and are known by those in the chemical industry and pharmaceutical industry. The quality of the optically active gossypols that are obtained can be controlled conveniently by means of their specific optical activity.

The (+) and (-) optically active gossypol that is provided by the method of this invention can be used in studying the antifertility activity, toxic action and mechanism of action of gossypol. (-) gossypol added to excipients or carriers suitable for medicinal drugs can be used for the treatment of female uterine myoma, dystopy of the endometrium, tumors of the endometrium, functional uterine hemorrhage and tumors such as leukemia. In addition, it can be used as a raw material for preparing derivatives to serve as antitumorigenic agent and antiviral drugs.

We shall now provide a more specific description of this invention:

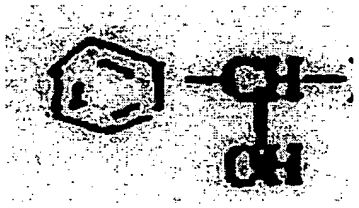
This invention provides method I for preparing optically active gossypol through of breakdown from racemic gossypol or a mixture of unequal amounts of (+) and (-) gossypol. In this method, the amine that is used to break down the racemic gossypol or mixture of unequal amounts of (+) and (-) gossypol is a monoamine type primary amine having levorotary or dextrorotary optical activity. It is characterized by having one or more than one [illegible] carbon, and, normally located at the α carbon, β carbon or other carbon, a portion of it can be represented by the following formula:

$$R_1\text{-}\underset{\displaystyle R_2}{\underset{|}{CH}}\text{-}NH_2$$

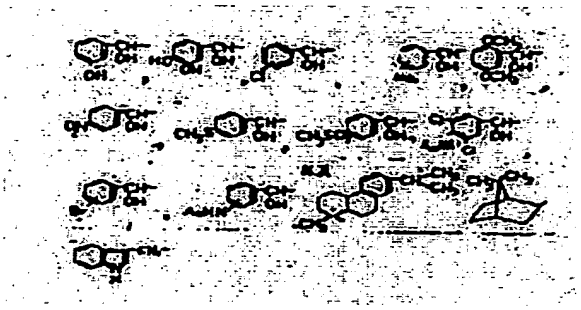
in which R_1 includes –H, CH_3, $-C_2H_5$ or other alkyl groups, $-CH_2-OH$, $-COOCH_3$, $-COOC_2H_6$ and other aldehyde groups. R_2 includes

and other substituted benzyl groups on the aromatic ring,

$$-CH_2-OH_2,\ -\underset{\displaystyle OH}{\underset{|}{CH}}\text{-}CH_3,\ -\underset{\displaystyle OH}{\underset{|}{CH}}\text{-}CH_2\text{-}CH_3,$$



and other substituted a-hydroxybenzyl groups on he aromatic ring, e.g.



The optically active amines or racemes listed above can be purchased on the market or can be synthesized by known methods or by general chemical methods similar to known methods. Both the R and S optically active isomers can be used and the raceme can be broken down using the d or l [illegible] salt-forming method or the preferential crystallization method. The methods of synthesis that can be used are described below. In these methods, there may or may not be substituted groups on the aromatic ring (for example, CH_3, OCH_3, -OH, -Cl, -Br, -I, -NHAc, $-NO_2$, $-SCH_3$, $-SO_2CH_3$, etc.).

1. $R\text{-}CHCH_2\text{-}OH$ (with NO_2 on the CH) ---- catalytic hydrogenation reduction or chemical reduction ----→ $R\text{-}CHCH_2\text{-}OH$ (with NH_2 on the CH)

R can include $-CH_3$, $-C_2H_5$, $-C_3H_7$, etc.

See U.S. Pat. 2174242

J. Org. Chem. 87 (1943)

2. $R\text{-}CH(NH_2Ar)\text{-}COOCH_3$ ---- catalytic hydrogenation reduction or Na + CH_3OH ----→ $R\text{-}CH(NH_2Ar)\text{-}CH_2\text{-}OH$

See J.A.C.S. 69 3039 (1947)

3. $R\text{-}CH(Ar)X\text{-}COOC_2H_6$ ---- NH_3EtOH ----→ $R\text{-}CH(Ar)NH_2\text{-}COOC_2H_5$

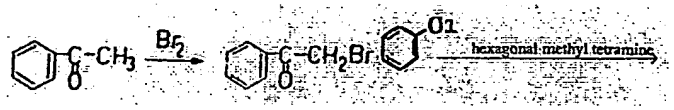
(X = halogens such as Cl, Br, etc.)

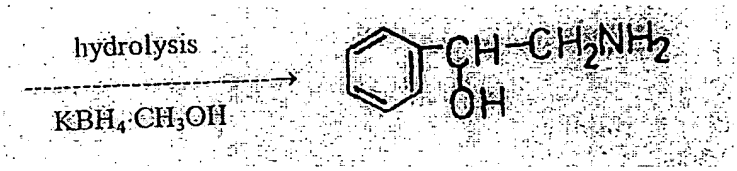
4. $R\text{-}\underset{\underset{(Ar)O}{||}}{C}\text{-}CH_3 \rightarrow R\text{-}\underset{\underset{(Ar)\ NH\ (N\text{-}OH)}{||}}{C}\text{-}CH_3 \dashrightarrow R\text{-}\underset{\underset{(Ar)\ \ NH_2}{|}}{CH}\text{-}CH_3$

$$R\text{-}CH_2\text{-}\underset{\underset{(Ar)\quad O\ (Ar)}{||}}{C}\text{-}CH_3 \rightarrow R\text{-}CH_2\text{-}\underset{\underset{NOH}{||}}{C}\text{-}CH_2 \xrightarrow{\text{reduction}} R\text{-}CH_2\text{-}\underset{\underset{(Ar)\qquad NH_2}{|}}{CH}\text{-}CH_3$$

See Org. Syn. Coll. Vol. III 717

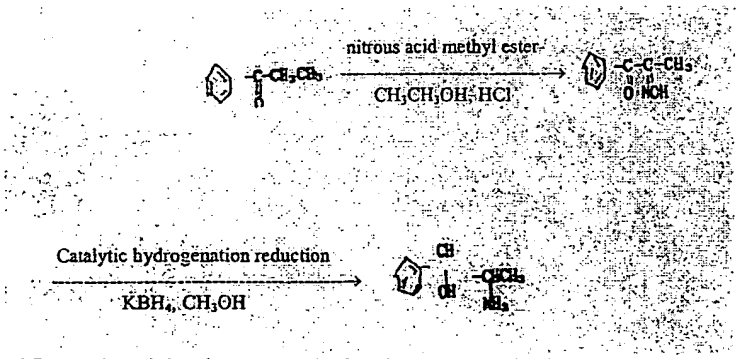
5.





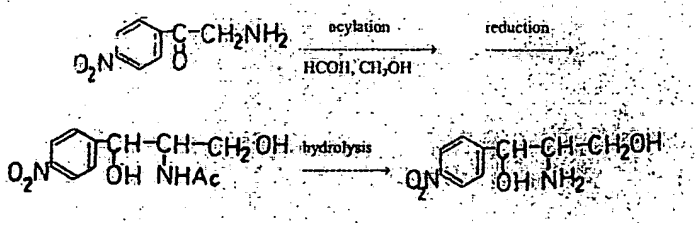
See J.A.C.S. 53 4149. (1931)

6.



See "National Raw Materials Pharmaceutical Industry Compilation," P, 495 (1980)

7.



See "National Raw Materials Pharmaceutical Industry Compilation," P-60 (1980)

Of the optically active amines described above, the more desirable amines are those having polar groups, for example, hydroxyl groups, [illegible], amines of halogens (fluorine, chlorine, bromine and

iodine), for example, optically active 1-(4-[illegible]-2-fluoro-propanol-1,3,3-hydroxy-phenylpropylamine-2, methyl phenylpropylamine, 1-hydroxy-phenylpropylamine-2 and 1-(4-aminophenyl)-2-amino-glycerol-1,3.

This technology can be understood by general technicians in this field. The optical purity of the optically active amines that are used when breaking down (+) and (-) gossypol is the major factor in determining the level of optical purity of the (+) or (-) gossypol after breakdown. In order to obtain optically active gossypol of a high degree of purity, optically active amines of a correspondingly high optical purity should be used during breakdown. The optical purity ee% of the optically active amines used in this invention is generally 98% or greater. However, specialists can select optically active amines of different optical purity on the basis of their own specific requirements. The solvent used in the condensation reaction can be a polar organic solvent, including alcohols, for example, methanol, ethanol, isopropionic alcohol, n-butyl alcohol and tert.-butyl alcohol; and ethers, for example,ethyl ether, tetrahydrofuran, dioxacyclohexane, monomethyl ether or monoethyl ether, dimethyl ether and diethyl ether. Nonpolar solvents can also be used, for example, benzene, hexane and cyclohexane.

The temperature of the condensation reaction described in this invention can be selected between room temperature and the boiling point of the solvent. Desirable temperatures are between 40 and 85°C.

Relying on the magnitude of difference (magnitude of the ΔR_f values) between the chromatograph R_f values of the reduced optical activity diastereomers of optically active amines of (+) and (-) gossypol obtained on the basis of this invention and on differences in their solubility in solvents and of the different chemical and optical stability of the condensates, mixtures of diastereomers can be separated using chromatography or the crystallization method.

The chromatographic methods discussed in this invention include normal pressure column, medium pressure column chromatography and high pressure column chromatography. The fillers that are used in them are silica gel, aluminum oxide, cellulose, polyamide octadecane group or ion exchange bonds. The preferable layer filler is silica gel.

The eluant can be selected on the basis of the differences of the R_f values of the condensate on the thin layer chromatogram. In general, ordinary solvents can be used, including hydrocarbons, for example, hexane, cyclohexane and benzene; ethers, for example, ethyl ether, petroleum ether and diozacyclohexane; chlorinated paraffins, for example, dichloromethane, trichloromethane and trichlroethane; esters, for example, ethyl acetate,and alcohols, for example, ethanol. Single systems or mixed systems of the aforementioned solvents can be used, with the use of mixed systems being preferable.

The wash solution is monitored by chromatography. Thin layer chromatography or high-pressure liquid chromatography can be used. It can be performed more conveniently by thin layer chromatography. The conditions used are the following. A thin layer made of silica gel, aluminum oxide or cellulose is used. The substances that can be used as developers are ethers, for example, ethyl ether, petroleum ether, dioxacyclohexane and tetrhydrofuran; hydrocarbons, for example, hexane, cyclohexane and benzene; and esters, for example ethyl acetate. A single solvent or mixtures of solvents can be used.

When the crystallization method is used to separate diastereomers, the mixture of optically active diastereomers of (+) and (-) gossypol obtained in the condensation reaction is subjected to crystallization in a suitable solvent. The solvents used can include hydrated or nonhydrated alcohols, for example the hydrated or nonhydrated alcohols listed below: methanol, ethanol, propanol, isopropanol and n-butyl alcohol; ethers, for example, ethyl ether, petroleum ether, tetrahydrofuran and dioxacyclohexane; hydrocarbons, for example, hexane, cyclohexane and benzene; chlroinated alkanes, for example, dichloromethane, chloroform and dichloroethane; esters, for example, ethyl acetate, and mixtures of the aforementioned solvents. The preferred solvents are alcohols.

On the basis of the method of this invention, condensed optically active diastereomers of (+) gossypol and (-) gossypol amine are hydrolyzed in a solvent in the presence of a catalyst, with optically active (+) or (-) gossypol being obtained. The hydrolysis solvents that can be used include hydrocarbons, for example, benzene, hexane and cyclohexane; ethers, for example, ethyl ether, petroleum ether, tetrahydrofuran and dioxacycohexane; ketones, for example, acetone and methyl ethyl ketone; chlorinated hydrocarbons, for example, dichloromethane and chloroform; alcohols, for example, methanol and ethanol; and mixtures or hydrated mixtures of two or more of the aforementioned solvents. Hydrated mixtures of the aforementioned solvents are preferable.

Catalysts that can be used are acids, including strong organic acids, for example, formic acid, acetic acid and p-toluenesulfonic acid; inorganic acids, for example, nitric acid, hydrochloric acid and sulfuric acid; and various cation exchange resins. Individual acids or mixtures of several types of acids can be used. Desirable acids are hydrochloric acid, sulfuric acid and acetic acid. Hydrochloric acid and hydrochloric acid – acetic acid mixtures are preferable.

The hydrolysis temperature can be between room temperature and 80°C.

The hydrolysis reaction can be monitored using thin layer chromatography. Selection of conditions can be the same as for monitoring thin layer chromatography during thin layer chromatographic separation.

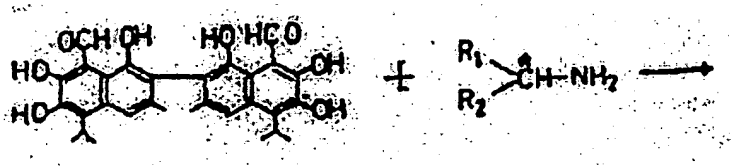
After hydrolysis, the organic layer is successively washed to a neutral state using an alkali, for example, potassium sulfate and sodium hydrogen sulfate and water. Crystallization is performed immediately after the solvent has been removed or after decoloration. The crystallization solvents that can be used include: hydrocarbons, for example, hexane, cyclohexane and benzene; ethers, for example, ethyl ether, petroleum ether and dioxacyclohexane; hydrated or nonhydrated alcohols, for example, hydrated or nonhydrated alcohols from the following list, methanol, ethanol, propanol, isopropanol and n-butyl alcohol; and mixed systems of two or more of the aforementioned solvents. The preferred solvents are mixed solvents such as ethyl ether – petroleum ether and benzene—petroleum ether. Under general conditions, the required optically active gossypol of optical purity and chemical purity greater than 90% can be obtained by a single crystallization. However, the optical purity of crystals that have been reprecipitated after a single crystallization is often decreased. For this reason, when necessary, the optically active gossypol that has been obtained can be subjected to further crystallization. Selection of the solvent can be the same as solvent selection for crystallization. After further separation of the optically active gossypol and the racemic gossypol, the chemical purity of the optically active gossypol that is obtained is assessed by high pressure liquid chromatography. [Chemical purity] of more than 99% can be reached. Optical purity can reach more than 97% on assessment by the specific rotation method and the high pressure liquid chromatography method.

In order to recover the decomposed reagents, the water layer component of the hydrolysis solution is mercerized with a strong alkali, causing the decomposition reagent to release the optically active amine, after which it is recovered by filtration or the solvent extraction method. Suitable alkalis that can be used include ammonium hydroxide, sodium hydroxide or potassium hydroxide solution.

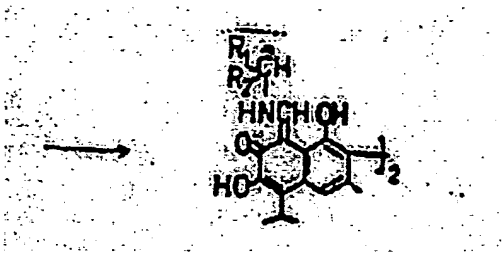
On the basis of the method of this invention, the stability of the condensed optically active amines of (+) gossypol and (-) gossypol is tested by single phase of double phase thin layer chromatography. Developers suitable for this test method that can be selected are ordinary organic solvents including ethyl ether, petroleum ether, dioxacyclohexane, hexane, cyclohexane, benzene, ethyl acetate and dichloromethane as single solutions or a mixed solutions of two or more of them. Suitable absorbent carriers that can be used are silica gel, aluminum oxide, cellulose and polyamides. After first phase drying, second phase developing is performed.

We shall now use Figure I to further explain method 1 that is provided in this invention.

Figure 1



I. Racemic gossypol II. Primary amine of the R or S monoamine type



III. (+) gossypol optically active R or S condensed amine compound and (-)gossypol optically active R or S condensed amine compound

Chromatograhic separation method
- High pressure liquid chromatography
- Medium pressure liquid chromatography
- Normal pressure liquid Chromatography

or crystal separation method

(+) Gossypol condensed optically active R or S amine compound	(-) Gossypol condensed optically active R or S amine compound
↓ hydrolysis	↓ hydrolysis
(+) gossypol	(-) gossypol

This invention also provides method II for preparing any one type of optically active gossypol to the maximum limit by conversion between (+) and (-) gossypol condensed optically active diastereomers and hydrolysis. The reaction solvents suited for the conversion of any one type of optically active gossypol condensed optically active amine provided in this invention to other diastereomers can be ordinary organic solvents, including ethers, for example, ethyl ether, petroleum ether, dioxacyclohexane and tetrahydrofuran; hydrocarbons, for example, benzene, hexane and cyclohexane; halogen-substituted alkanes, for example, dichloromethane, chloroform, dichloroethane and trichloroethane; ketones, for example, acetone and methyl ethyl ketone; alcohols, for example, methanol, ethanol, propanol and isopropanol as single solvents or as mixtures of several solvents.

Suitable catalysis conditions include indirectly irradiated sunlight, ultraviolet irradiation or introduction of free radical promoters, for example, 2,2'-azobis-2-methylpropionic [illegible].

The temperature for conversion can be selected from room temperature to 70°C as desired.

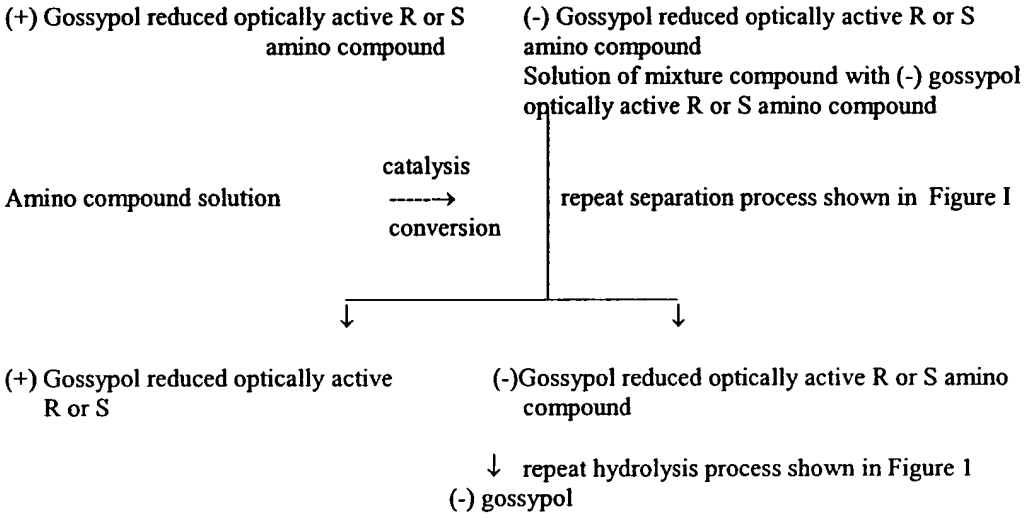
Conversion time is determined by the specific optically active amine that is used in preparing the condensate, the ratio of the various isomers in the condensate mixture that is use during conversion and the

conversion conditions and the specific requirements for degree of conversion. Generally, it can be from several minutes to several days. Good optically active amines used for conversion in this invention are S-1- methylphenylamine, (+) dehydrogenated amine and (+) –1-hydroxyphenylpropylamine-2.

Separation and hydrolysis conditions of the condensate diastereomer mixture after conversion and crystallization conditions are the same as selected in method I of this invention.

Figure II below is a further explanation of method II provided by this invention:

Figure II



The conversion process required for conversion of (-) gossypol shown in Figure II or a similar process can be used as conversion conditions for (+) gossypol.

This invention also provides method III, which is a precipitation method, for obtaining the optically active gossypol of the highest content to the maximum extent possible from mixtures containing unequal amounts of (+) and (-) gossypol. In which suitable acids for producing 1 : 1 composite precipitate solutions of equal amounts of (+) gossypol and (-) gossypol include low molecular weight organic acids such as formic acid and acetic acid. The amount used can be varied within a comparatively large range. However, the lowest amount cannot be lower than the quantity of moles of gossypol in the solvent.

Suitable solvent that can be used when the composite that is produced is precipitated are ordinary organic solvents including ethers, for example, ethyl ether, petroleum ether, dioxacyclohexane and tetrahydrofuran; alkanes, for example, hexane, cyclohexane and benzene; halogen substituted paraffins, for example, dichloromethane, chloroform, dichloroethane and trichloroethane; ketones, for example, acetone and methyl ethyl ketone; esters, for example, ethyl acetate; alcohol, for example, methanol, ethanol, propanol and isopropanol, with the preferential solvents being ethyl ether, acetone and dichloromethane.

The reaction temperature is better to be from room temperature to 50°C.

Figure III below further explains method III provided by this invention.

Figure III

Racemic gossypol + (+) gossypol or racemic gossypol + (-) gossypol

| dissolved in the solvent
| add appropriate amount of acid

↓ ↓

Racemic gossypol and composite formed of acid (precipitate)

Excess quantity of (+) gossypol or (-) gossypol with remaining acid

↓ neutralization, extraction
(+) gossypol or (-) gossypol

We shall now present a further explanation of this invention by means of examples. However, this invention is not limited by them.

Examples

Examples 1 to 4. Preparation of optically active gossypol from racemic gossypol using the breakdown method.

Example 1. Preparation of optically active gossypol by breaking down racemic gossypol using threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 as the breakdown agent

Preparation of gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3:

24 g (0.046 mol) of racemic gossypol and 22.5 g (0.106 mol) of threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 were heated and refluxed for 10 to 15 minutes in 50 ml of acetone, the reaction solution was then cooled to room temperature, the solvent was removed and 41.7 g of condensate was obtained. The yield was 100%. Elemental analysis: Racemic gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 ($C_{48}H_{60}N_4O_{14}\cdot 2H_2O$; molecular weight, 942.9)

	Theoretical value %	Experimental value %	
C	61.14	61.09	61.03
H	5.77	5.65	5.61
N	5.94	6.32	6.35

$[a]_D^{20°} = -240 \pm 20$ (acetone)

Separation of gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 by normal pressure column chromatography:

A crude product of the above mentioned substance was separated under normal pressure using a silicic acid column layer, and, using ethyl ether as the eluent, 19 g (45.6% (calculated as the theoretical amount)

of (-) gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 (A), $[a]_D^{20°} = -930 \pm 30$ (acetone), and 17 g (40.8%) of (+) gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 (B) could be obtained, $[a]_D^{20°} = -$[illegible] ± 20 could be obtained. Yield, 86.4%.

Separation of gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 by the crystallization method:

10 g (0.0193 mol) of racemic gossypol and 9.6 g (0.0447 mol) of threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 were stirred, heated and refluxed for 10 to 15 minutes in 50 ml of methanol, after which they were allowed to stand at low temperature, with a yellow solid being precipitated. 6.3 g of (-) gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 (A), $[a]_D^{20°} = -930 \pm 30$ was obtained. The calculated yield for racemic gossypol was 36% and the calculated yield of 50% (-1) gossypol in the racemic gossypol was 72%.

The mother liquor was poured into water and yellow solid was obtained. It was filtered and weighed 12 g. It was a mixture consisting primarily of (+) gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 (B) and a small quantity of (A). $[a]_D^{17°} = 120 \pm 20$ (acetone). The content of B was about 75%. Total yield was 98%.

Hydrolysis of (-) gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 to (-) gossypol:

6 g (0.006 mol) of (-) gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 was suspended in 200 ml of ethyl ether containing 20 ml of glacial acetic acid and 16 ml of a nonperoxide of concentrated sulfuric acid and the mixture was stirred, heated and refluxed for 4 hours. The reaction solution was then cooled to room temperature and the acid solution layer was separated. (Optically active amine can be recovered by treating the dehydrated layer with an alkali.) The ether layer was washed with water and was washed to a neutral state with potassium carbonate. It was then dried, with some of the solvent being removed. A suitable quantity of petroleum ether was added and the mixture was allowed to stand at room temperature, with crystals being precipitated out. The crystals were filtered and 1.65 g of needle-shaped light yellow crystals could be obtained. After the mother liquor was concentrated, 1.28 g of similar crystals could be obtained. The yield was 85%. The product was recrystallized, after which a product of a melting point of 185~7°C and of $[a]_D^{20°} = 360 \pm 10$ (chloroform) was obtained and determined to be (-) gossypol. MS: 518 (M^+), 500, 482, 467, 454, 329, 226, 205, 150, 149. Chemical purity > 99% (HPLC). Optical purity ee% > 98.8% (HPLC).

Hydrolysis of (+)gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 to (+) gossypol:

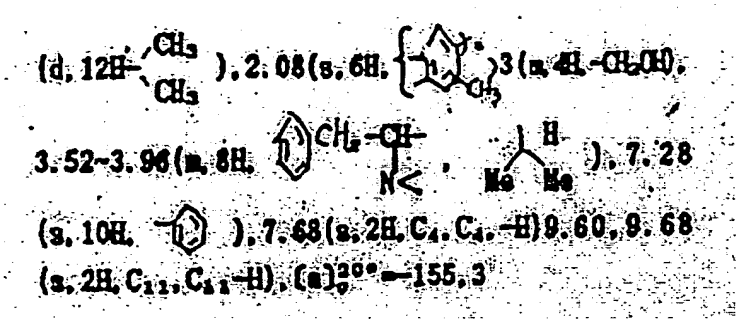
17.5 g (0.0186 mol) of (+) gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 was hydrolyzed under conditions similar to those described above and 9.5 g of crude product was obtained. It was decolorized by passing it through a silica gel column chromatography device, after which 4.27 g of crystals were obtained. The yield was 44%. It was then recrystallized, a product of a melting point of 185~7°C and of $[a]_D^{20°} = 360 \pm 10$ (chloroform) was obtained. Chemical purity > 99% (HPLC). Optical purity ee% > 97% (HPLC).

Example 2. Preparation of optically active gossypol by breakdown of racemic gossypol using L-3-hydroxy-phenylpropanolamine-2 as the decomposition agent

Preparation of racemic gossypol L-3-hydroxy-phenylpropanolamine-2:

3 g (0.0058 mol) of racemic gossypol was dissolved in 150 ml of isopropanol and 20 ml of a solution containing 2.6 g (0.0174 mol) of L-3-hydroxy-phenylpropanolamine-2-isopropanol was added under stirring. Heating and reflux were performed for 5 to 10 minutes, the reaction solution was cooled to room temperature and the solvent was removed. The product was crystallized in an ethyl ether-petroleum ether

mixed solvent. 2.72 g of crude product was obtained. HNMR ($CDCl_3$) 90Hz.
δ: 1.52



(chloroform). Melting point, 140-142°C.

The condensate indicated above can be use in a procedure similar to that in Example 1. Separation was performed under normal pressure by silica gel column chromatography. The separated matter that was obtained was (-) gossypol condensed L-3-hydroxy-phenylpropanolamine-2 of $[a]_D^{20°} = -849.2$ (chloroform). (-) gossypol could be obtained by hydrolysis. (+) gossypol could be obtained by hydrolyzing the other separation product.

Example 3. Preparation of optically active gossypol by breakdown of racemic gossypol using S-a-methyl benzylamine as the decomposition agent

Preparation of racemic gossypol condensed S-a-methyl benzylamine

0.5 g (0.004 mol) of S-a-methyl benzylamine (98%) and 1.04 g (0.002 mol) of racemic gossypol were mixed in 50 ml of ethyl ether and the mixture was heated and refluxed for 10 minutes. The reaction solution was cooled to room temperature, the solvent was removed and 1.3 g of condensate was obtained. Yield, 86.4%. Elemental analysis:

$C_{46}H_{48}N_2O_6$. Molecular weight, 724.9

Calculated values %: C 76.22, H 6.69, N 3.86

Experimental values%: C 76.19, H 6.92, N 3.80

76.94, 6.66, 3.79

$[a]_D^{19°} = +53$ ($CHCL_3$). Melting point, 245~9°C.

Separation of racemic gossypol condensed S-a-methyl benzylamine by medium pressure column chromatography:

0.4 g of condensate was separated by medium pressure column chromatography using silica gel H as the filler. At a pressure was in the range of 2.5 to 3 kg/cm^2 and with a mixed solution of non-hydrated ethyl ether and petroleum ether as the eluent, 0.15 g of (+) gossypol condensed S-a-methyl benzylamine, $[a]_D^{17°} = +739$ ($CHCL_3$), and 0.13 g of (-) gossypol condensed S-a-methyl benzylamine, $[a]_D^{17°} = -643$ ($CHCL_3$) could be separated. The yield was greater than 70%.

Hydrolysis of (+) gossypol condensed S-a-methyl benzylamine to (+) gossypol

0.45 g of (+) gossypol condensed S-a-methyl benzylamine was suspended in 200 ml of a mixed solution

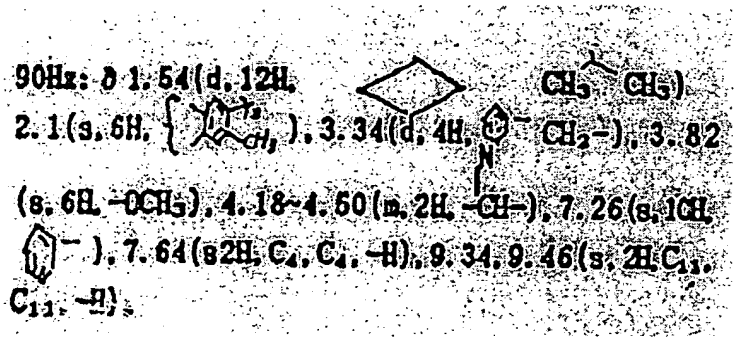
of ethyl ether – petroleum ether and a suitable quantity of dichloromethane was added to dissolve the solid, after which 3 ml of concentrated hydrochloric acid was added and the reaction solution was allowed to stand at room temperature for 1 to 2 days. The aqueous layer was removed from the reaction solution and the ether layer was washed with water to a neutral state and dried. The hydrolysate, which had been subjected to acid treatment, was decolorized by silica gel medium pressure chromatography and was crystallized using benzene-petroleum ether mixed solvent. 0.18 g of pale yellow needle shaped crystals were obtained. Melting point 183~5°C. $[a]_D^{15°} = +375.6$ ($CHCL_3$). The yield was 78.1%. Optical purity ee% > 96.8 (HPLC determined).

Example 4. Preparation of optically active gossypol by breakdown of racemic gossypol using L-benzyl propionic acid methyl ester as the decomposition agent

Preparation of racemic gossypol condensed L-benzyl phenylalaine methyl ester

An isopropanol-aqueous solution of 1.52 g(0.0071 mol) of L-benzyl phenylalanine methyl ester hydrochloride was introduced into a solution of 2 g (0.0039 mol) of racemic gossypol, an isopropanol-aqueous solution of 0.6 g (0.0043 mol) of potassium carbonate was added under stirring and heating and reflux were performed for 5 to 10 minutes. The reaction solution was cooled to room temperature, most of the reaction solvent was removed and a partial solid product was obtained. It weighed 2.22 g and the yield was 68.5%.

$[a]_D^{20°} = -327$ ($CHCl_3$), melting point 144-146°C, H-NMR ($CDCl_3$)



The condensate indicated above can be used in a procedure similar to that in Example 3. Separation was performed under medium pressure by silica gel column chromatography. The separated matter that was obtained was (-) gossypol condensed L-benzyl phenylalanine ester of $[a]_D^{20°} = -679.2$ ($CHCl_3$). (-) gossypol could be obtained by hydrolysis. (+) gossypol could be obtained by hydrolyzing the other separation product.

In Examples 5 to 7, optically active gossypol was prepared by conversion between gossypol condensed optically active diastereomers and hydrolysis.

In Example 5, optically active gossypol was prepared using S-1-methyl phenyl acetic acid as the decomposition agent by conversion between diastereomers of gossypol condensed optically active amine and hydrolysis.

Preparation of racemic gossypol condensed S-1-methyl phenylacetic acid:

9 g (0.066 mol) of S-1-methyl phenylacetic acid was introduced under stirring into a 500 ml isopropanol solution of 11.6 g (0.02 mol) of gossypol and was heated to boiling for 5 to 10 minutes. The reaction solution was cooled to room temperature and its concentration was crystallized, after which 14 g of product could be obtained. The yield was 99%. $[a]_D^{24°} = +222.9$ ($CHCl_3$). Melting point, 197~200°C.

Elemental analysis:
$C_{43}H_{62}N_2O_6$.

Calculated values %: C 76.57, H 6.96, N 3.73

Experimental values %: C 76.66, H 7.00, N 3.59

76.62, 7.00, 3.58

The condensates indicated above can be separated by medium pressure column chromatography using a procedure similar to that of Example 3. They included (+) gossypol condensed S-1-methyl phenylalanine, $[a]_D^{15°} = +931$ ($CHCl_3$), and (-) gossypol condensed S-1 methyl phenylalanine $[a]_D^{30°} = -400$ ($CHCl_3$).

(+) gossypol condensed S-1-methyl phenylalanine was converted to a 1 : 1 mixture of (+) gossypol condensed S-1 methyl phenylalanine and (-)gossypol condensed S-1-methyl phenylalanine.

(+) gossypol condensed S-1-methyl phenylalanine, $[a]_D^{15°} = +931$ ($CHCl_3$), was dissolved in ethyl ether-petroleum ether mixed solvent, the solution was allowed to stand at room temperature without avoiding light for 1 to 2 days (direct irradiation with sunlight being avoided) and a mixture of (+) gossypol condensed S-1-methyl phenylalanine and (-) gossypol S-1-methyl phenylalanine of $[a]_D^{30°} = +242$ ($CHCl_3$) could be obtained.

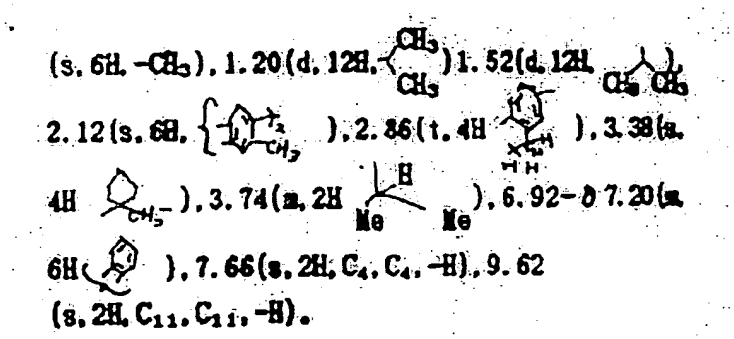
By a similar method, (-) gossypol condensed S-1-methyl phenylalanine, $[a]_D^{15°} = -400$ ($CHCl_3$), can be converted to mixture of condensate diastereomers of $[a]_D^{30°} = +203.2$ ($CHCl_3$).

By again separating the mixture by medium pressure column chromatography after the transformation described above, any one desirable diastereomer in the condensate can again be obtained, and, by hydrolysis under conditions like those of Example 3, corresponding optically active gossypols can be obtained.

In Example 6, optically active gossypol was prepared by converting racemic condensed gossypol to [illegible] optically active diastereomer using (+) dehydrogenated amine as the decomposition agent and hydrolysis.

Preparation of racemic condensed gossypol (+) dehydrogenated amine:

0.3 g (0.0006 mol) of racemic condensed gossypol was dissolved in 30 ml of isopropyl alcohol and 0.0378 g (0.0013 mol) of (+) dehydrogenated amine. Heating and reflux were performed for 10 minutes under stirring, the reaction solution was allowed to stand at room temperature and was concentrated, after which it was allowed to stand and crystallize. 0.355 g of product was obtained. Yield, 60%. $[a]_D^{20°} = -13.9$ ($CHCl_3$). Melting point, 211-213°C. HNMR ($CDCl_3$) 90 Hz: δ: 1.0

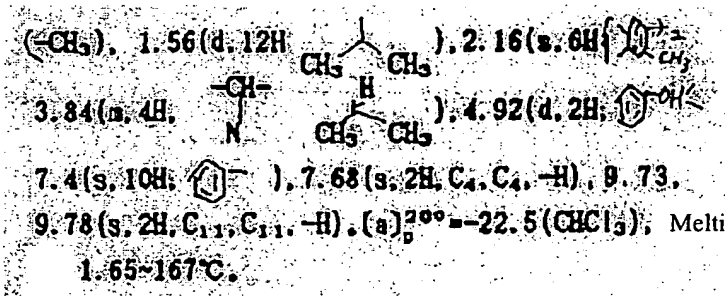


The condensate indicated above was used in medium pressure column chromatography under conditions like those in Example 3 and good (-) gossypol condensed (+) dehydrogenated amine could be obtained. $[a]_D^{19°} = -560.4$ ($CHCl_3$). Hydrolysis was performed under the same hydrolysis conditions as in Example 3 and (-) gossypol could be obtained. A mixture of unseparated (-) gossypol condensed (+) dehydrogenated amine and (+) gossypol condensed (+) dehydrogenated amine could be converted under the same conversion conditions as in Example 5. A mixture was obtained in which the ratio of converted (-) gossypol condensed (+) dehydrogenated amine and (+) gossypol condensed (+) dehydrogenated amine was close to 1 : 1. In addition, more (-) gossypol condensed (+) dehydrogenated amine was separated by again performing medium pressure column chromatography, with even more (-) gossypol being obtained after hydrolysis.

In Example 7, optically active gossypol was obtained using (+)-1-hydroxy-phenylalanine-2 as the decomposition agent by conversion and hydrolysis of racemic gossypol condensed optically active diastereomers.

Preparation of racemic gossypol condensed (+)-1-hydroxy-phenylalanine-2:

1.59 g (8.49×10^{-3} mol) of (+)-1-hydroxy-phenylalanine-2 hydrochloride and 0.59 g (4.3×10^{-3} mol) of potassium carbonate were mixed, a small quantity of water was added to dissolve them and free amine was extracted with ethyl ether. The extraction solution was added to an isopropanol solution with racemic gossypol content of 2 g (3.86×10^{-3} mol) and heating and reflux were performed for 5 to 10 minutes under stirring. The reaction solution was cooled to room temperature, the solvent was removed and crystallization was effected in ethyl ether-water. The amount of crystals obtained the first time was 1.4 g. Yield, 47%. HNMR[illegible] ($CDCl_3$), δ: 1.30 (d, 6H,



The aforementioned condensate was used for separation by medium pressure column chromatography under conditions similar to those in Example 3 and good (+) gossypol condensed (+)-1-hydroxyphenylalanine-2 and (-)gossypol 1-hydroxyphenylalanine-2 could be obtained. Good (-)gossypol 1-hydroxyphenylalanine-2 was present in the incompletely separated mixture components in an amount of 74%. $[a]_D^{20°} = -529.4$ ($CHCl_3$). By separating this component and converting it by the same conversion method as in Example 5, a mixture of $[a]_D^{20°} = -26.9$ ($CHCl_3$) containing the two types of diasteromer in a ratio of 1 : 1 could be obtained. When this mixture was again subjected to medium pressure column chromatography, a (+) gossypol condensate and a (-) gossypol condensate could be obtained. The separated products was hydrolyzed under the same conditions as in Example 3 and (+) gossypol and (-) gossypol could be obtained.

Examples 8 and 9. Methods of preparing any desired individual type of optically active gossypol to the maximum extent from mixtures of unequal amounts of (+) and (-) gossypol using the acid precipitation method.

Example 8. Extraction of optically pure (+) gossypol from a hydrolyzed product containing 75% of (+) gossypol condensate by the acetic acid precipitation method:

12 g (0.0132 mol), $[a]_D^{20°} = +120 \pm 20$ (acetone) of a content of about 75% of (+) gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 (B) (for preparation method and separation method, see Example 1) was hydrolyzed by the method of Example 1. The ether layer was washed to a neutral state, after which it was dried and concentrated. 5 ml of glacial acetic acid was added , it was allowed to stand at a low temperature and 2.65 g of a composite of acetic acid and racemic gossypol was precipitated. The mother liquor was washed with sodium hydrogen carbonate solution and was washed with water to a neutral state, after which it was dried and decolorized silica gel column chromatography, by which means 1.9 g of needle-shaped crystals was obtained, $[a]_D^{15°} = +353$ ($CHCl_3$), melting point, 185~7°C as (+) gossypol. The yield of crystals from first time was 43% (calculated for content of (+) gossypol). (+) gossypol could also be obtained by concentrating the crystallized mother liquor.

Example 9. Preparation of optically active (+) gossypol in a commercial gossypol product containing unequal amounts of (+) gossypol and (-) gossypol by the acetic acid precipitation method.

A small quantity of ethyl ether solution was added to 3 g of gossypol product and the mixture was filtered, after which 10 ml of glacial acetic acid was added. The mixture was allowed to stand until a solid was precipitated. A mixture with acetic acid and racemic gossypol was formed and filtered, filtered solution was washed with sodium hydrogen carbonate solution to a neutral state. It was extracted with ethyl ether and dried, after which it was decolorized by column chromatography and crystallized in a mixed solution of benzene and petroleum ether, with 70 mg of needle-shaped crystals being obtained. $[a]_D^{17°} = +369.8$ ($CHCl_3$); melting point, 185~7°C.

Figure I

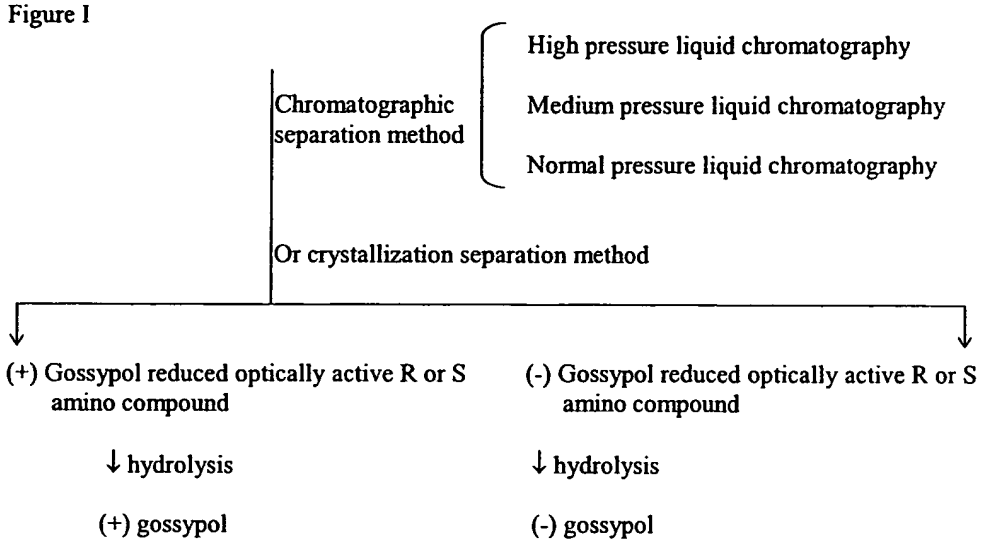


Figure II

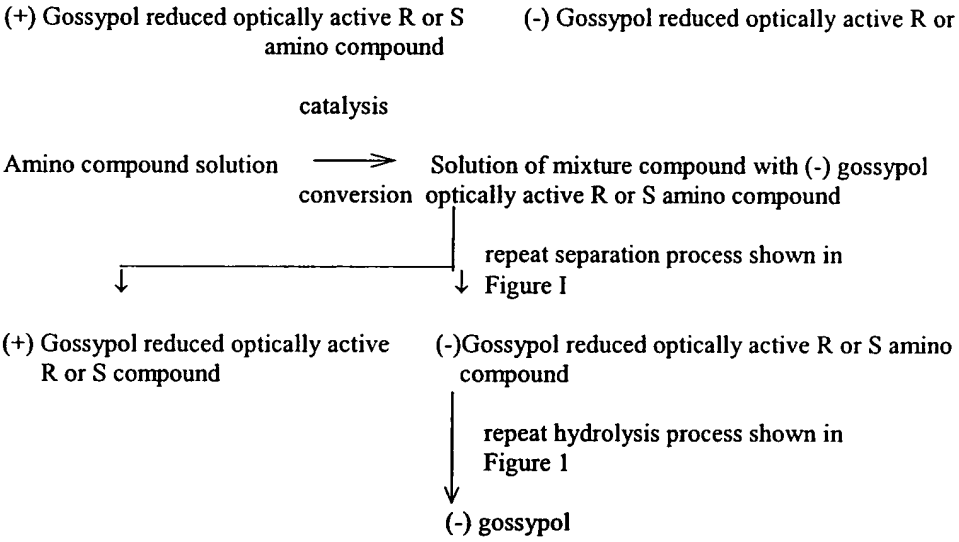
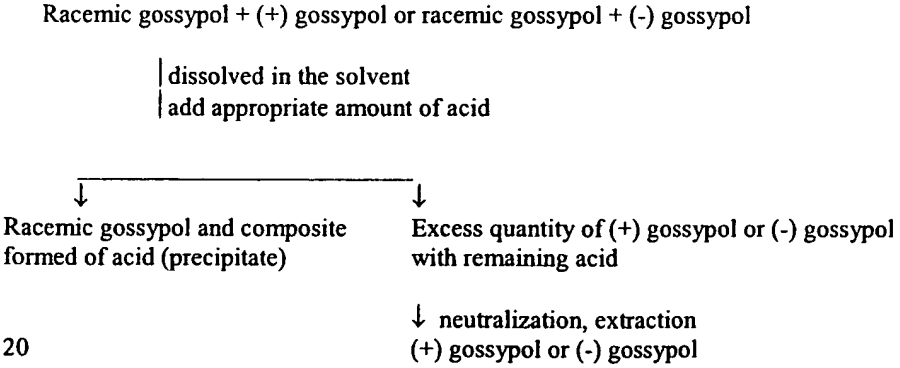


Figure III



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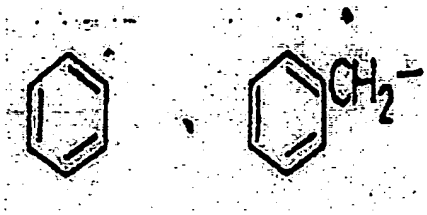
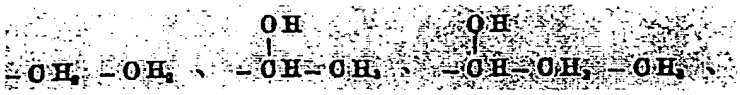
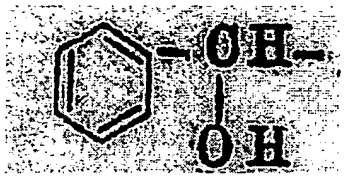
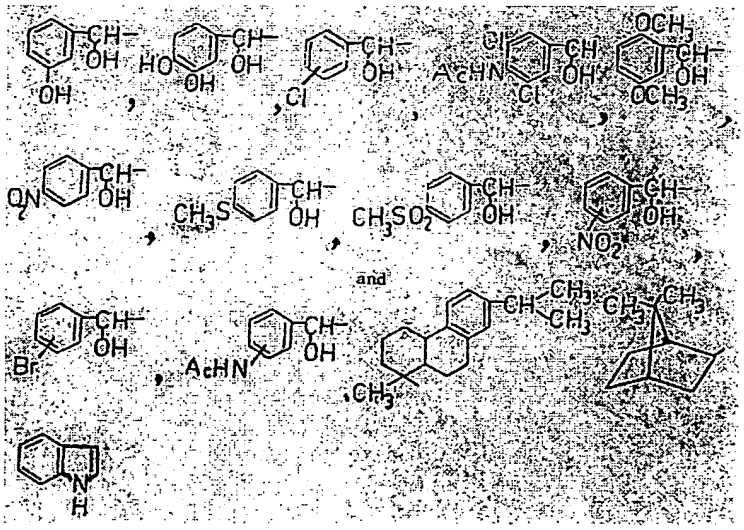


and benzyl groups with other substituted groups on the aromatic ring.

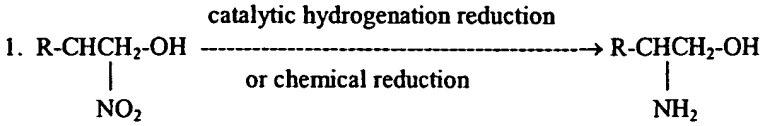




and a-hydroxybenzyl groups with other substituted groups on the aromatic ring, e.g.



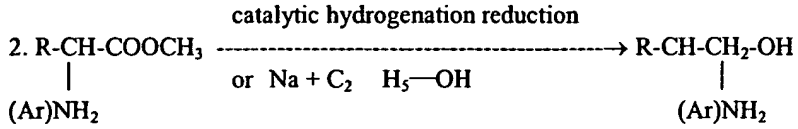
The optically active amines or racemic forms indicated above can be purchased on the market or can be obtained by general chemical synthetic method similar to known methods. The two optical isomers R and S can be used and the racemic form can be broken down using the method of salt formation of d or l tartaric acid or can be broken down using the preferential crystallization method. A method of analysis that can be used is presented below. There may be or may not be other substituted groups on the aromatic ring (for example, CH_3, OCH_3, -OH, -Cl, -Br, -I, -NHAc, $-NO_2$, $-SCH_3$, $-SO_2CH_3$, etc.)



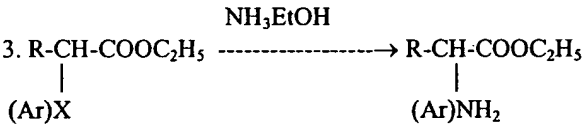
R can include –CH_6, -$C2H_5$, -$C3H_7$ etc.

See U.S. Pat, 2174242

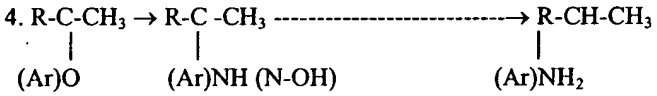
J. Org. Chem. 8 7(1943)

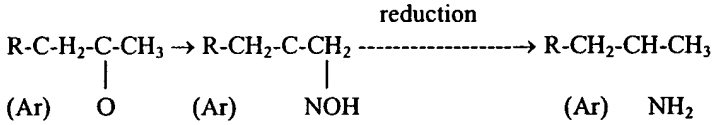


See J.A.C.S. 69 3039 (1947)



(X = halogens such as Cl, Br)





See Org. Syn. Coll. Vol. III 717

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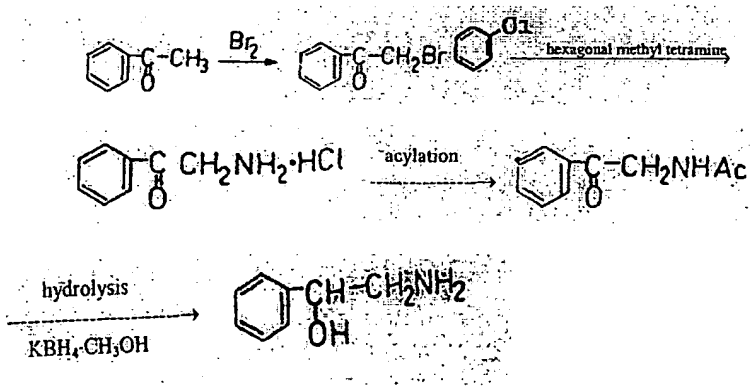

See J.A.C.S. 53 4149, (1931)

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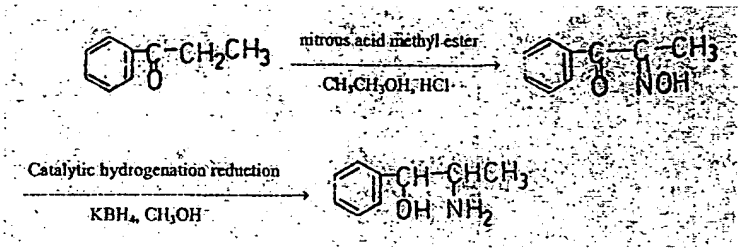

See "National Raw Materials and Pharmaceutical Technology Compendium," P. 495 (1980)

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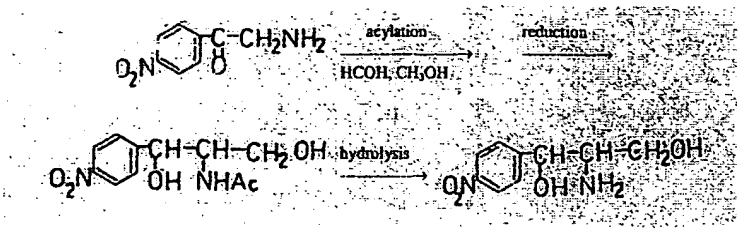


See "National Raw Materials and Pharmaceutical Technology Compendium," P. 60 (1980)

Of the optically active amines described above, the more desirable amines are those having polar groups, for example, hydroxyl groups, [illegible], amines of halogens (fluorine, chlorine, bromine and iodine), for example, optically active 1-(4-[illegible]-2-fluoro-propanol-1,3,3-hydroxy-phenylpropylamine-2, methyl phenylpropylamine, 1-hydroxy-phenylpropylamine-2 and 1-(4-aminophenyl)-2-amino-glycerol-1,3.

This technology can be understood by general technicians in this field. The optical purity of the optically active amines that are used when breaking down (+) and (-) gossypol is the major factor in determining the level of optical purity of the (+) or (-) gossypol after breakdown. In order to obtain optically active gossypol of a high degree of purity, optically active amines of a correspondingly high optical purity should be used during breakdown. The optical purity ee% of the optically active amines used in this invention is generally 98% or greater. However, specialists can select optically active amines of different optical purity on the basis of their own specific requirements. The solvent used in the condensation reaction can be a polar organic solvent, including alcohols, for example, methanol, ethanol, isopropionic alcohol, n-butyl alcohol and tert.-butyl alcohol; and ethers, for example,ethyl ether, tetrahydrofuran, dioxacyclohexane, monomethyl ether or monoethyl ether, dimethyl ether and diethyl ether. Nonpolar solvents can also be used, for example, benzene, hexane and cyclohexane.

The temperature of the condensation reaction described in this invention can be selected between room temperature and the boiling point of the solvent. Desirable temperatures are between 40 and 85°C.

Relying on the magnitude of difference (magnitude of the ΔR_f values) between the chromatograph R_f values of the reduced optical activity diastereomers of optically active amines of (+) and (-) gossypol obtained on the basis of this invention and on differences in their solubility in solvents and of the different chemical and optical stability of the condensates, mixtures of diastereomers can be separated using chromatography or the crystallization method.

The chromatographic methods discussed in this invention include normal pressure column, medium pressure column chromatography and high pressure column chromatography. The fillers that are used in

them are silica gel, aluminum oxide, cellulose, polyamide octadecane group or ion exchange bonds. The preferable layer filler is silica gel.

The eluant can be selected on the basis of the differences of the R_f values of the condensate on the thin layer chromatogram. In general, ordinary solvents can be used, including hydrocarbons, for example, hexane, cyclohexane and benzene; ethers, for example, ethyl ether, petroleum ether and diozacyclohexane; chlorinated paraffins, for example, dichloromethane, trichloromethane and trichlroethane; esters, for example, ethyl acetate,and alcohols, for example, ethanol. Single systems or mixed systems of the aforementioned solvents can be used, with the use of mixed systems being preferable.

The wash solution is monitored by chromatography. Thin layer chromatography or high-pressure liquid chromatography can be used. It can be performed more conveniently by thin layer chromatography. The conditions used are the following. A thin layer made of silica gel, aluminum oxide or cellulose is used. The substances that can be used as developers are ethers, for example, ethyl ether, petroleum ether, dioxacyclohexane and tetrhydrofuran; hydrocarbons, for example, hexane, cyclohexane and benzene; and esters, for example ethyl acetate. A single solvent or mixtures of solvents can be used.

When the crystallization method is used to separate diastereomers, the mixture of optically active diastereomers of (+) and (-) gossypol obtained in the condensation reaction is subjected to crystallization in a suitable solvent. The solvents used can include hydrated or nonhydrated alcohols, for example the hydrated or nonhydrated alcohols listed below: methanol, ethanol, propanol, isopropanol and n-butyl alcohol; ethers, for example, ethyl ether, petroleum ether, tetrahydrofuran and dioxacyclohexane; hydrocarbons, for example, hexane, cyclohexane and benzene; chlroinated alkanes, for example, dichloromethane, chloroform and dichloroethane; esters, for example, ethyl acetate, and mixtures of the aforementioned solvents. The preferred solvents are alcohols.

On the basis of the method of this invention, condensed optically active diastereomers of (+) gossypol and (-) gossypol amine are hydrolyzed in a solvent in the presence of a catalyst, with optically active (+) or (-) gossypol being obtained. The hydrolysis solvents that can be used include hydrocarbons, for example, benzene, hexane and cyclohexane; ethers, for example, ethyl ether, petroleum ether, tetrahydrofuran and dioxacycohexane; ketones, for example, acetone and methyl ethyl ketone; chlorinated hydrocarbons, for example, dichloromethane and chloroform; alcohols, for example, methanol and ethanol; and mixtures or hydrated mixtures of two or more of the aforementioned solvents. Hydrated mixtures of the aforementioned solvents are preferable.

Catalysts that can be used are acids, including strong organic acids, for example, formic acid, acetic acid and p-toluenesulfonic acid; inorganic acids, for example, nitric acid, hydrochloric acid and sulfuric acid; and various cation exchange resins. Individual acids or mixtures of several types of acids can be used. Desirable acids are hydrochloric acid, sulfuric acid and acetic acid. Hydrochloric acid and hydrochloric acid – acetic acid mixtures are preferable.

The hydrolysis temperature can be between room temperature and 80°C.

The hydrolysis reaction can be monitored using thin layer chromatography. Selection of conditions can be the same as for monitoring thin layer chromatography during thin layer chromatographic separation.

After hydrolysis, the organic layer is successively washed to a neutral state using an alkali, for example, potassium sulfate and sodium hydrogen sulfate and water. Crystallization is performed immediately after the solvent has been removed or after decoloration. The crystallization solvents that can be used include: hydrocarbons, for example, hexane, cyclohexane and benzene; ethers, for example, ethyl ether, petroleum ether and dioxacyclohexane; hydrated or nonhydrated alcohols, for example, hydrated or nonhydrated alcohols from the following list, methanol, ethanol, propanol, isopropanol and n-butyl alcohol; and mixed systems of two or more of the aforementioned solvents. The preferred solvents are mixed solvents such as ethyl ether – petroleum ether and benzene—petroleum ether. Under general conditions, the required optically active gossypol of optical purity and chemical purity greater than 90% can be obtained by a single crystallization. However, the optical purity of crystals that have been reprecipitated after a single

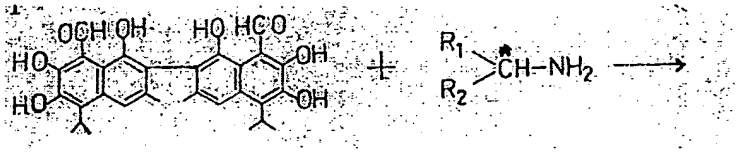
crystallization is often decreased. For this reason, when necessary, the optically active gossypol that has been obtained can be subjected to further crystallization. Selection of the solvent can be the same as solvent selection for crystallization. After further separation of the optically active gossypol and the racemic gossypol, the chemical purity of the optically active gossypol that is obtained is assessed by high pressure liquid chromatography. [Chemical purity] of more than 99% can be reached. Optical purity can reach more than 97% on assessment by the specific rotation method and the high pressure liquid chromatography method.

In order to recover the decomposed reagents, the water layer component of the hydrolysis solution is mercerized with a strong alkali, causing the decomposition reagent to release the optically active amine, after which it is recovered by filtration or the solvent extraction method. Suitable alkalis that can be used include ammonium hydroxide, sodium hydroxide or potassium hydroxide solution.

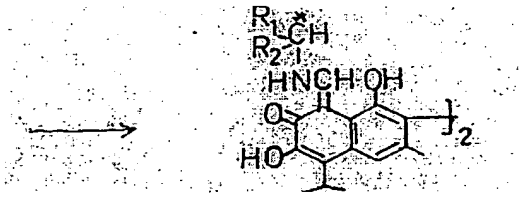
On the basis of the method of this invention, the stability of the condensed optically active amines of (+) gossypol and (-) gossypol is tested by single phase of double phase thin layer chromatography. Developers suitable for this test method that can be selected are ordinary organic solvents including ethyl ether, petroleum ether, dioxacyclohexane, hexane, cyclohexane, benzene, ethyl acetate and dichloromethane as single solutions or a mixed solutions of two or more of them. Suitable absorbent carriers that can be used are silica gel, aluminum oxide, cellulose and polyamides. After first phase drying, second phase developing is performed.

We shall now use Flow Chart I to further explain method 1 that is provided in this invention.

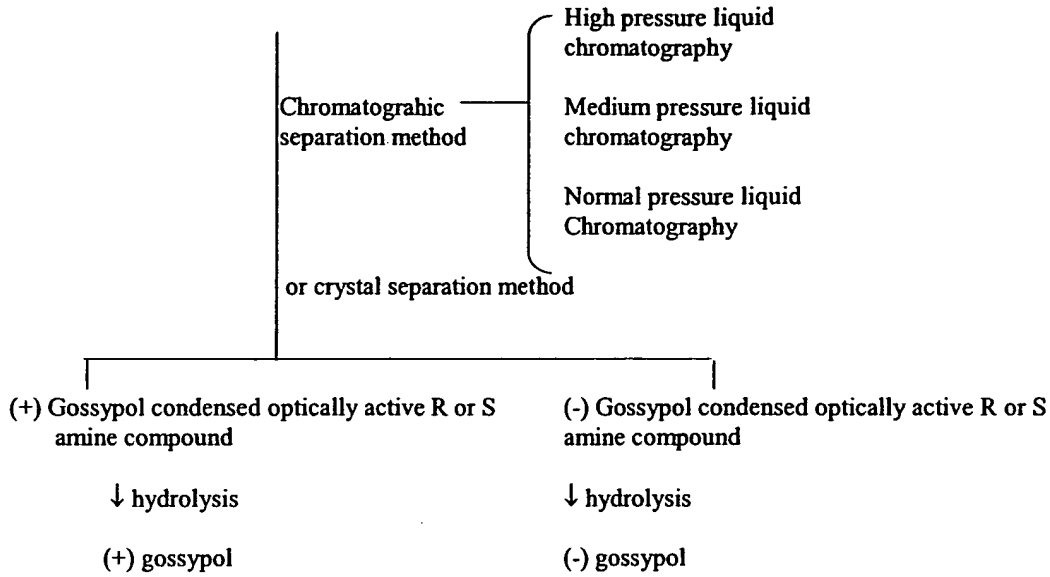
Flow Chart I



I. Racemic gossypol II. Primary amine of the R or S monoamine type



III. (+) gossypol optically active R or S condensed amine compound and (-)gossypol optically active R or S condensed amine compound



This invention also provides method II for preparing any one type of optically active gossypol to the maximum limit by conversion between (+) and (-) gossypol condensed optically active diastereomers and hydrolysis. The reaction solvents suited for the conversion of any one type of optically active gossypol condensed optically active amine provided in this invention to other diastereomers can be ordinary organic solvents, including ethers, for example, ethyl ether, petroleum ether, dioxacyclohexane and tetrahydrofuran; hydrocarbons, for example, benzene, hexane and cyclohexane; halogen-substituted alkanes, for example, dichloromethane, chloroform, dichloroethane and trichloroethane; ketones, for example, acetone and methyl ethyl ketone; alcohols, for example, methanol, ethanol, propanol and isopropanol as single solvents or as mixtures of several solvents.

Suitable catalysis conditions include indirectly irradiated sunlight, ultraviolet irradiation or introduction of free radical promoters, for example, 2,2'-azobis-2-methylpropionic [illegible].

The temperature for conversion can be selected from room temperature to 70°C as desired.

Conversion time is determined by the specific optically active amine that is used in preparing the condensate, the ratio of the various isomers in the condensate mixture that is use during conversion and the

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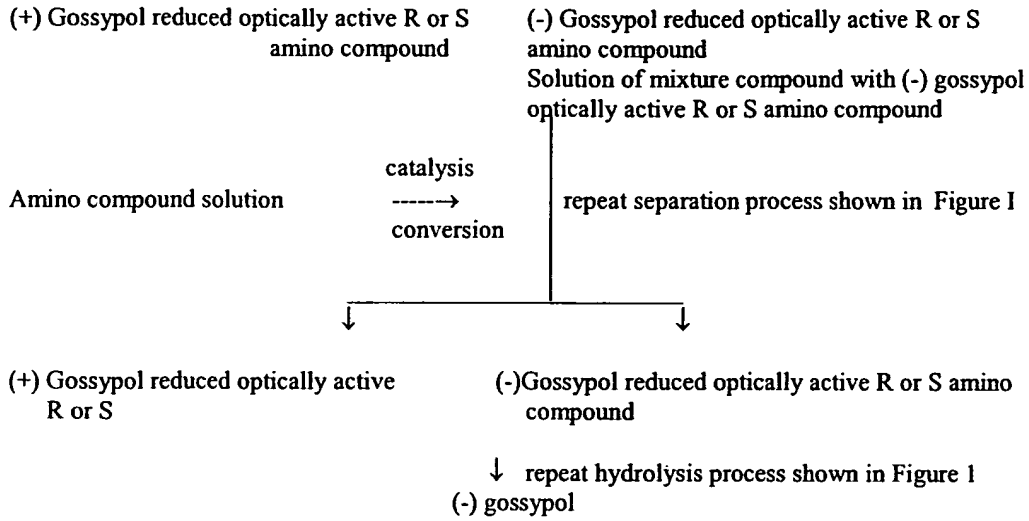
conversion conditions and the specific requirements for degree of conversion. Generally, it can be from several minutes to several days. Good optically active amines used for conversion in this invention are S-1- methylphenylamine, (+) dehydrogenated amine and (+) -1-hydroxyphenylpropylamine-2.

Separation and hydrolysis conditions of the condensate diastereomer mixture after conversion and crystallization conditions are the same as selected in method I of this invention.

Flowchart II below is a further explanation of method II provided by this invention:

Flowchart II



Flowchart II demonstrated the conversion process of (-) gossypol needed, a similar process can be used for conversion of (+) gossypol.

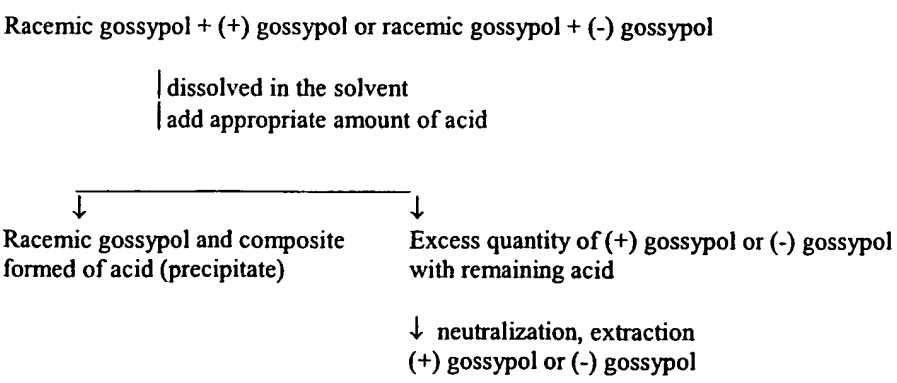
This invention also provides method III, which is a precipitation method, for obtaining the optically active gossypol of the highest content to the maximum extent possible from mixtures containing unequal amounts of (+) and (-) gossypol. In which suitable acids for producing 1 : 1 composite precipitate solutions of equal amounts of (+) gossypol and (-) gossypol include low molecular weight organic acids such as formic acid and acetic acid. The amount used can be varied within a comparatively large range. However, the lowest amount cannot be lower than the quantity of moles of gossypol in the solvent.

Suitable solvent that can be used when the composite that is produced is precipitated are ordinary organic solvents including ethers, for example, ethyl ether, petroleum ether, dioxacyclohexane and tetrahydrofuran; alkanes, for example, hexane, cyclohexane and benzene; halogen substituted paraffins, for example, dichloromethane, chloroform, dichloroethane and trichloroethane; ketones, for example, acetone and methyl ethyl ketone; esters, for example, ethyl acetate; alcohol, for example, methanol, ethanol, propanol and isopropanol, with the preferential solvents being ethyl ether, acetone and dichloromethane.

The reaction temperature is better to be from room temperature to 50°C.

Flowchart III below further explains method III provided by this invention.

Flowchart III



We shall now present a further explanation of this invention by means of examples. However, this invention is not limited by them.

Examples

Examples 1 to 4. Preparation of optically active gossypol from racemic gossypol using the breakdown method.

Example 1. Preparation of optically active gossypol by breaking down racemic gossypol using threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 as the breakdown agent

Preparation of gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3:

24 g (0.046 mol) of racemic gossypol and 22.5 g (0.106 mol) of threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 were heated and refluxed for 10 to 15 minutes in 50 ml of acetone, the reaction solution was then cooled to room temperature, the solvent was removed and 41.7 g of condensate was obtained. The yield was 100%. Elemental analysis: Racemic gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 ($C_{48}H_{60}N_4O_{14}\cdot 2H_2O$; molecular weight, 942.9)

	Theoretical value %	Experimental value %	
C	61.14	61.09	61.03
H	5.77	5.65	5.61
N	5.94	6.32	6.35

$[a]_D^{20^\circ} = -240 \pm 20$ (acetone)

Separation of gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 by normal pressure column chromatography:

A crude product of the above mentioned substance was separated under normal pressure using a silicic acid column layer, and, using ethyl ether as the eluent, 19 g (45.6% (calculated as the theoretical amount) 13 of (-) gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 (A), $[a]_D^{20^\circ} = -930 \pm 30$ (acetone), and 17 g (40.8%) of (+) gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 (B) could be obtained, $[a]_D^{20^\circ}$ = -[illegible] ± 20 could be obtained. Yield, 86.4%.

Separation of gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 by the crystallization method:

10 g (0.0193 mol) of racemic gossypol and 9.6 g (0.0447 mol) of threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 were stirred, heated and refluxed for 10 to 15 minutes in 50 ml of methanol, after which they were allowed to stand at low temperature, with a yellow solid being precipitated. 6.3 g of (-) gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 (A), $[a]_D^{20^\circ} = 930 \pm 30$ was obtained. The calculated yield for racemic gossypol was 36% and the calculated yield of 50% (-1) gossypol in the racemic gossypol was 72%.

The mother liquor was poured into water and yellow solid was obtained. It was filtered and weighed 12 g. It was a mixture consisting primarily of (+) gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-

glycerol-1,3 (B) and a small quantity of (A). $[a]_D^{17°} = 120 \pm 20$ (acetone). The content of B was about 75%. Total yield was 98%.

Hydrolysis of (-) gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 to (-) gossypol:

6 g (0.006 mol) of (-) gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 was suspended in 200 ml of ethyl ether containing 20 ml of glacial acetic acid and 16 ml of a nonperoxide of concentrated sulfuric acid and the mixture was stirred, heated and refluxed for 4 hours. The reaction solution was then cooled to room temperature and the acid solution layer was separated. (Optically active amine can be recovered by treating the dehydrated layer with an alkali.) The ether layer was washed with water and was washed to a neutral state with potassium carbonate. It was then dried, with some of the solvent being removed. A suitable quantity of petroleum ether was added and the mixture was allowed to stand at room temperature, with crystals being precipitated out. The crystals were filtered and 1.65 g of needle-shaped light yellow crystals could be obtained. After the mother liquor was concentrated, 1.28 g of similar crystals could be obtained. The yield was 85%. The product was recrystallized, after which a product of a melting point of 185~7°C and of $[a]_D^{20°} = 360 \pm 10$ (chloroform) was obtained and determined to be (-) gossypol. MS: 518 (M^+), 500, 482, 467, 454, 329, 226, 205, 150, 149. Chemical purity > 99% (HPLC). Optical purity ee% > 98.8% (HPLC).

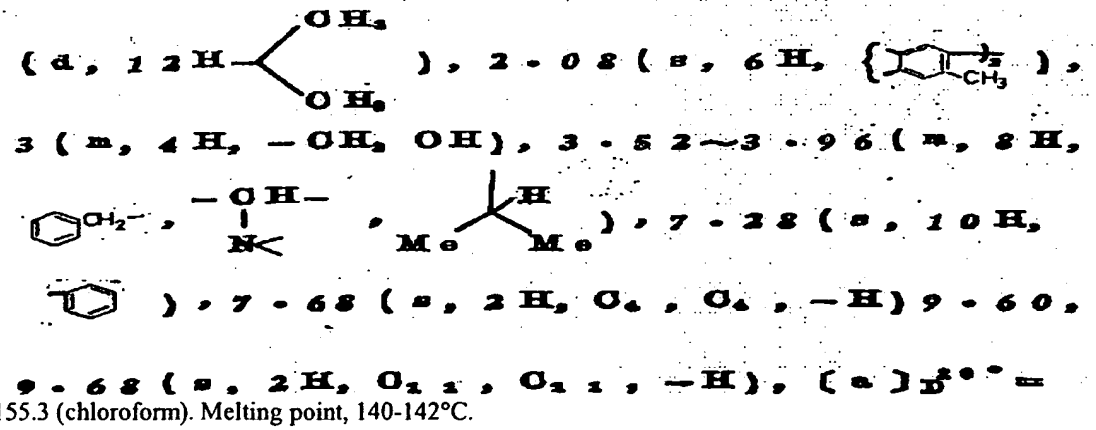
Hydrolysis of (+)gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 to (+) gossypol:

17.5 g (0.0186 mol) of (+) gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 was hydrolyzed under conditions similar to those described above and 9.5 g of crude product was obtained. It was decolorized by passing it through a silica gel column chromatography device, after which 4.27 g of crystals were obtained. The yield was 44%. It was then recrystallized, a product of a melting point of 185~7°C and of $[a]_D^{20°} = 360 \pm 10$ (chloroform) was obtained. Chemical purity > 99% (HPLC). Optical purity ee% > 97% (HPLC).

Example 2. Preparation of optically active gossypol by breakdown of racemic gossypol using L-3-hydroxy-phenylpropanolamine-2 as the decomposition agent

Preparation of racemic gossypol L-3-hydroxy-phenylpropanolamine-2:

3 g (0.0058 mol) of racemic gossypol was dissolved in 150 ml of isopropanol and 20 ml of a solution containing 2.6 g (0.0174 mol) of L-3-hydroxy-phenylpropanolamine-2-isopropanol was added under stirring. Heating and reflux were performed for 5 to 10 minutes, the reaction solution was cooled to room temperature and the solvent was removed. The product was crystallized in an ethyl ether-petroleum ether mixed solvent. 2.72 g of crude product was obtained. HNMR ($CDCl_3$) 90Hz, δ: 1.52



-155.3 (chloroform). Melting point, 140-142°C.

The condensate indicated above can be use in a procedure similar to that in Example 1. Separation was performed under normal pressure by silica gel column chromatography. The separated matter that was obtained was (-) gossypol condensed L-3-hydroxy-phenylpropanolamine-2 of $[a]_D^{20°} = -849.2$ (chloroform). (-) gossypol could be obtained by hydrolysis. (+) gossypol could be obtained by hydrolyzing the other separation product.

Example 3. Preparation of optically active gossypol by breakdown of racemic gossypol using S-a-methyl benzylamine as the decomposition agent

Preparation of racemic gossypol condensed S-a-methyl benzylamine

0.5 g (0.004 mol) of S-a-methyl benzylamine (98%) and 1.04 g (0.002 mol) of racemic gossypol were mixed in 50 ml of ethyl ether and the mixture was heated and refluxed for 10 minutes. The reaction solution was cooled to room temperature, the solvent was removed and 1.3 g of condensate was obtained. Yield, 86.4%. Elemental analysis:

$C_{46}H_{48}N_2O_6$. Molecular weight, 724.9

Calculated values %: C 76.22, H 6.69, N 3.86

Experimental values%: C 76.19, H 6.92, N 3.80

76.94, 6.66, 3.79

$[a]_D^{19°} = +53$ ($CHCL_3$). Melting point, 245~9°C.

Separation of racemic gossypol condensed S-a-methyl benzylamine by medium pressure column chromatography:

0.4 g of condensate was separated by medium pressure column chromatography using silica gel H as the filler. At a pressure was in the range of 2.5 to 3 kg/cm^2 and with a mixed solution of non-hydrated ethyl ether and petroleum ether as the eluent, 0.15 g of (+) gossypol condensed S-a-methyl benzylamine, $[a]_D^{17°} = +739$ ($CHCL_3$), and 0.13 g of (-) gossypol condensed S-a-methyl benzylamine, $[a]_D^{17°} = -643$ ($CHCL_3$) could be separated. The yield was greater than 70%.

Hydrolysis of (+) gossypol condensed S-a-methyl benzylamine to (+) gossypol

0.45 g of (+) gossypol condensed S-a-methyl benzylamine was suspended in 200 ml of a mixed solution of ethyl ether – petroleum ether and a suitable quantity of dichloromethane was added to dissolve the solid, after which 3 ml of concentrated hydrochloric acid was added and the reaction solution was allowed to stand at room temperature for 1 to 2 days. The aqueous layer was removed from the reaction solution and the ether layer was washed with water to a neutral state and dried. The hydrolysate, which had been subjected to acid treatment, was decolorized by silica gel medium pressure chromatography and was crystallized using benzene-petroleum ether mixed solvent. 0.18 g of pale yellow needle shaped crystals were obtained. Melting point 183~5°C. $[a]_D^{15°} = +375.6$ ($CHCL_3$). The yield was 78.1%. Optical purity ee% > 96.8 (HPLC determined).

Example 4. Preparation of optically active gossypol by breakdown of racemic gossypol using L-benzyl propionic acid methyl ester as the decomposition agent

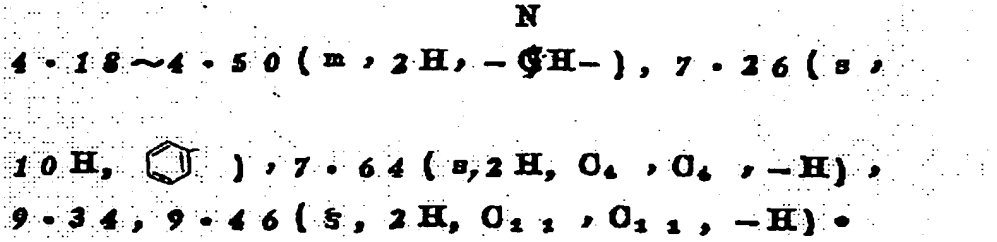
Preparation of racemic gossypol condensed L-benzyl phenylalaine methyl ester

An isopropanol-aqueous solution of 1.52 g(0.0071 mol) of L-benzyl phenylalanine methyl ester hydrochloride was introduced into a solution of 2 g (0.0039 mol) of racemic gossypol, an isopropanol-aqueous solution of 0.6 g (0.0043 mol) of potassium carbonate was added under stirring and heating and reflux were performed for 5 to 10 minutes. The reaction solution was cooled to room temperature, most of

the reaction solvent was removed and a partial solid product was obtained. It weighed 2.22 g and the yield was 68.5%.

$[a]_D^{20°}$ = -327 ($CHCl_3$), melting point 144-146°C,

^1H-NMR ($CDCl_3$), 90 HZ: δ 1.54 (d, 12H, CH_3 CH_3), 2.1 (s, 6H, ), 3.34 (d, 4H,  CH_2-), 3.82 (s, 6H, $-OCH_3$),



4.18~4.50 (m, 2H, -CH-), 7.26 (s, 10H,), 7.64 (s, 2H, C_4, C_4, -H), 9.34, 9.46 (s, 2H, C_{21}, C_{21}, -H).

The condensate indicated above can be used in a procedure similar to that in Example 3. Separation was performed under medium pressure by silica gel column chromatography. The separated matter that was obtained was (-) gossypol condensed L-benzyl phenylalanine ester of $[a]_D^{20°}$ = -679.2 ($CHCl_3$). (-) gossypol could be obtained by hydrolysis. (+) gossypol could be obtained by hydrolyzing the other separation product.

In Examples 5 to 7, optically active gossypol was prepared by conversion between gossypol condensed optically active diastereomers and hydrolysis.

In Example 5, optically active gossypol was prepared using S-1-methyl phenyl acetic acid as the decomposition agent by conversion between diastereomers of gossypol condensed optically active amine and hydrolysis.

Preparation of racemic gossypol condensed S-1-methyl phenylacetic acid:

9 g (0.066 mol) of S-1-methyl phenylacetic acid was introduced under stirring into a 500 ml isopropanol solution of 11.6 g (0.02 mol) of gossypol and was heated to boiling for 5 to 10 minutes. The reaction solution was cooled to room temperature and its concentration was crystallized, after which 14 g of product could be obtained. The yield was 99%. $[a]_D^{24°}$ = +222.9 ($CHCl_3$). Melting point, 197~200°C.

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Elemental analysis:

$C_{43}H_{62}N_2O_6$.

Calculated values %: C 76.57, H 6.96, N 3.73

Experimental values %: C 76.66, H 7.00, N 3.59

76.62, 7.00, 3.58

The condensates indicated above can be separated by medium pressure column chromatography using a procedure similar to that of Example 3. They included (+) gossypol condensed S-1-methyl phenylalanine, $[a]_D^{15°}$ = +931 ($CHCl_3$), and (-) gossypol condensed S-1 methyl phenylalanine $[a]_D^{30°}$ = -400 ($CHCl_3$).

(+) gossypol condensed S-1-methyl phenylalanine was converted to a 1 : 1 mixture of (+) gossypol condensed S-1 methyl phenylalanine and (-)gossypol condensed S-1-methyl phenylalanine.

(+) gossypol condensed S-1-methyl phenylalanine, $[a]_D^{15°} = +931$ ($CHCl_3$), was dissolved in ethyl ether-petroleum ether mixed solvent, the solution was allowed to stand at room temperature without avoiding light for 1 to 2 days (direct irradiation with sunlight being avoided) and a mixture of (+) gossypol condensed S-1-methyl phenylalanine and (-) gossypol S-1-methyl phenylalanine of $[a]_D^{30°} = +242$ ($CHCl_3$) with a ratio close to 1:1 could be obtained.

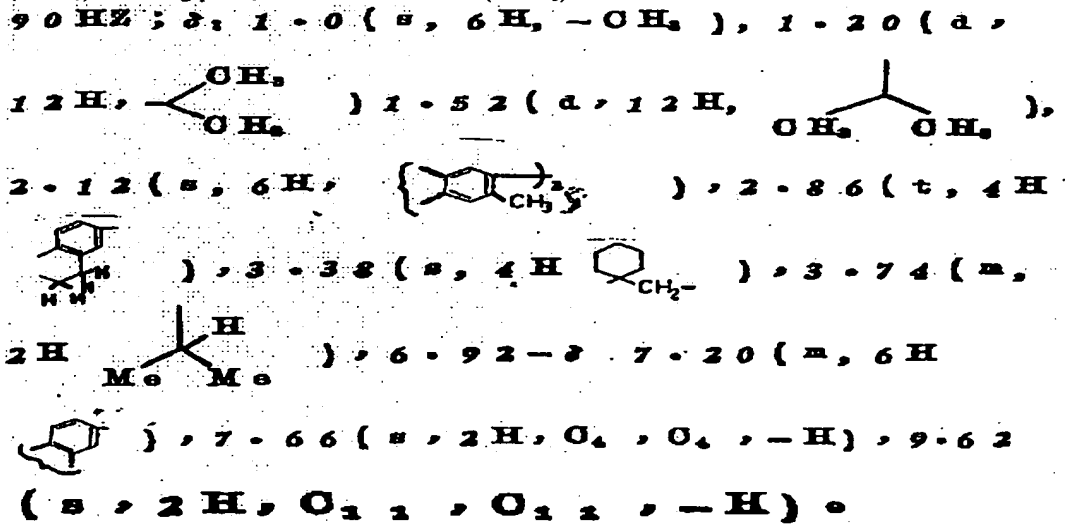
By a similar method, (-) gossypol condensed S-1-methyl phenylalanine, $[a]_D^{15°} = -400$ ($CHCl_3$), can be converted to mixture of condensate diastereomers of $[a]_D^{30°} = +203.2$ ($CHCl_3$).

By again separating the mixture by medium pressure column chromatography after the transformation described above, any one desirable diastereomer in the condensate can again be obtained, and, by hydrolysis under conditions like those of Example 3, corresponding optically active gossypols can be obtained.

In Example 6, optically active gossypol was prepared by converting racemic condensed gossypol to [illegible] optically active diastereomer using (+) dehydrogenated amine as the decomposition agent and hydrolysis.

Preparation of racemic condensed gossypol (+) dehydrogenated amine:

0.3 g (0.0006 mol) of racemic condensed gossypol was dissolved in 30 ml of isopropyl alcohol and 0.0378 g (0.0013 mol) of (+) dehydrogenated amine. Heating and reflux were performed for 10 minutes under stirring, the reaction solution was allowed to stand at room temperature and was concentrated, after which it was allowed to stand and crystallize. 0.355 g of product was obtained. Yield, 60%. $[a]_D^{20°} = -13.9$ ($CHCl_3$). Melting point, 211-213°C. HNMR ($CDCl_3$)



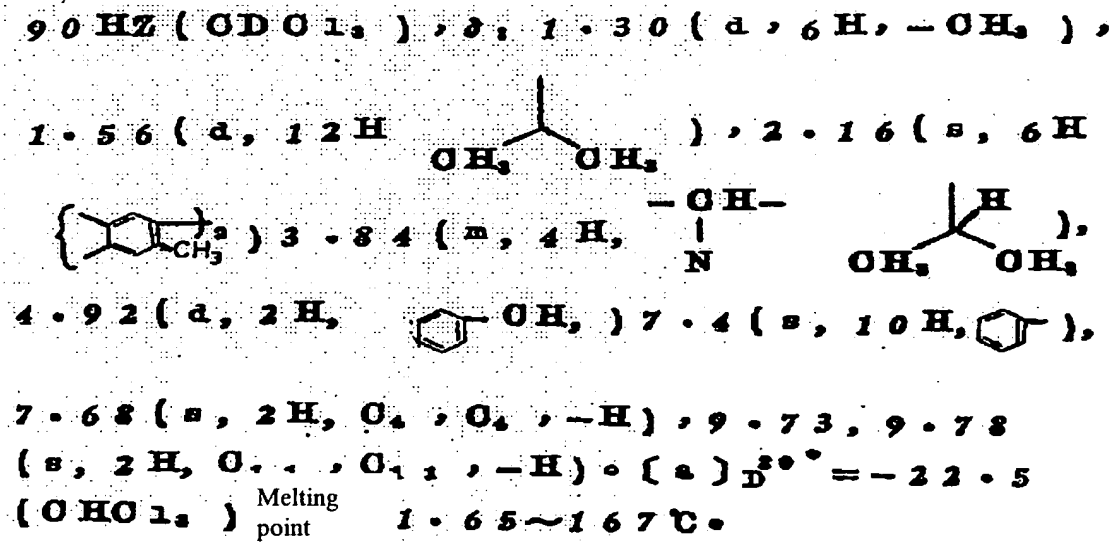
The condensate indicated above was used in medium pressure column chromatography under conditions like those in Example 3 and good (-) gossypol condensed (+) dehydrogenated amine could be obtained. $[a]_D^{19°} = -560.4$ ($CHCl_3$). Hydrolysis was performed under the same hydrolysis conditions as in Example 3 and (-) gossypol could be obtained. A mixture of unseparated (-) gossypol condensed (+) dehydrogenated amine and (+) gossypol condensed (+) dehydrogenated amine could be converted under the same conversion conditions as in Example 5. A mixture was obtained in which the ratio of converted (-) gossypol condensed (+) dehydrogenated amine and (+) gossypol condensed (+) dehydrogenated amine

was close to 1 : 1. In addition, more (-) gossypol condensed (+) dehydrogenated amine was separated by again performing medium pressure column chromatography, with even more (-) gossypol being obtained after hydrolysis.

In Example 7, optically active gossypol was obtained using (+)-1-hydroxy-phenylalanine-2 as the decomposition agent by conversion and hydrolysis of racemic gossypol condensed optically active diastereomers.

Preparation of racemic gossypol condensed (+)-1-hydroxy-phenylalanine-2:

1.59 g (8.49×10^{-3} mol) of (+)-1-hydroxy-phenylalanine-2 hydrochloride and 0.59 g (4.3×10^{-3} mol) of potassium carbonate were mixed, a small quantity of water was added to dissolve them and free amine was extracted with ethyl ether. The extraction solution was added to an isopropanol solution with racemic gossypol content of 2 g (3.86×10^{-3} mol) and heating and reflux were performed for 5 to 10 minutes under stirring. The reaction solution was cooled to room temperature, the solvent was removed and crystallization was effected in ethyl ether-water. The amount of crystals obtained the first time was 1.4 g. Yield, 47%. HNMR



The aforementioned condensate was used for separation by medium pressure column chromatography under conditions similar to those in Example 3 and good (+) gossypol condensed (+)-1-hydroxyphenylalanine-2 and (-)gossypol 1-hydroxyphenylalanine-2 could be obtained. Good (-)gossypol 1-hydroxyphenylalanine-2 was present in the incompletely separated mixture components in an amount of 74%. $[a]_D^{20°} = -529.4$ ($CHCl_3$). By separating this component and converting it by the same conversion method as in Example 5, a mixture of $[a]_D^{20°} = -26.9$ ($CHCl_3$) containing the two types of diasteromer in a ratio of 1 : 1 could be obtained. When this mixture was again subjected to medium pressure column chromatography, a (+) gossypol condensate and a (-) gossypol condensate could be obtained. The separated products was hydrolyzed under the same conditions as in Example 3 and (+) gossypol and (-) gossypol could be obtained.

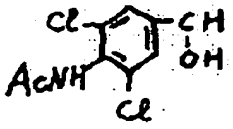
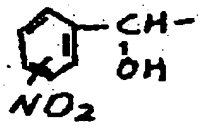
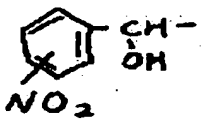
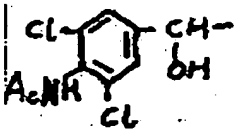
Examples 8 and 9. Methods of preparing any desired individual type of optically active gossypol to the maximum extent from mixtures of unequal amounts of (+) and (-) gossypol using the acid precipitation method.

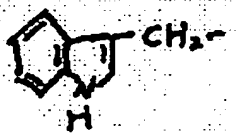
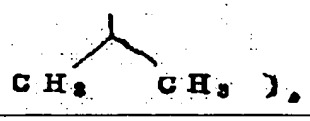
Example 8. Extraction of optically pure (+) gossypol from a hydrolyzed product containing 75% of (+) gossypol condensate by the acetic acid precipitation method:

12 g (0.0132 mol), $[a]_D^{20°} = +120 \pm 20$ (acetone) of a content of about 75% of (+) gossypol condensed threo (-)-1-(p-nitrobenzene)-2-amino-glycerol-1,3 (B) (for preparation method and separation method, see Example 1) was hydrolyzed by the method of Example 1. The ether layer was washed to a neutral state, after which it was dried and concentrated. 5 ml of glacial acetic acid was added , it was allowed to stand at a low temperature and 2.65 g of a composite of acetic acid and racemic gossypol was precipitated. The mother liquor was washed with sodium hydrogen carbonate solution and was washed with water to a neutral state, after which it was dried and decolorized silica gel column chromatography, by which means 1.9 g of needle-shaped crystals was obtained, $[a]_D^{15°} = +353$ ($CHCl_3$), melting point, 185~7°C as (+) gossypol. The yield of crystals from first time was 43% (calculated for content of (+) gossypol). (+) gossypol could also be obtained by concentrating the crystallized mother liquor.

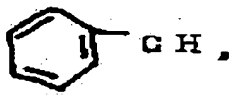
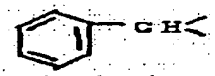
Example 9. Preparation of optically active (+) gossypol in a commercial gossypol product containing unequal amounts of (+) gossypol and (-) gossypol by the acetic acid precipitation method.

A small quantity of ethyl ether solution was added to 3 g of gossypol product and the mixture was filtered, after which 10 ml of glacial acetic acid was added. The mixture was allowed to stand until a solid was precipitated. A mixture with acetic acid and racemic gossypol was formed and filtered, filtered solution was washed with sodium hydrogen carbonate solution to a neutral state. It was extracted with ethyl ether and dried, after which it was decolorized by column chromatography and crystallized in a mixed solution of benzene and petroleum ether, with 70 mg of needle-shaped crystals being obtained. $[a]_D^{17°} = +369.8$ ($CHCl_3$); melting point, 185~7°C.

(4) Name of document	Page	Line	Before correction	After correction
Specification	3	3-4	III. A method for extracting optically active gossypol of higher content to the maximum extent from mixtures containing different amounts of (+) and (-) gossypol by the acid precipitation method.	III. A mixture of antipodes containing unequal amounts of (+) gossypol and (-) gossypol and a method for removing the antipode of lesser content and for obtaining the antipode of higher optical purity and content by the precipitation method using an acid that can form a 1 : 1 composite precipitate with racemic gossypol.
	3	5-14	Specifically speaking ..... a method for obtaining antipodes of higher optical purity and content,	(delete)
	4	13	Contain	(eliminate)
	4	13	Element	between elements
	4	16	Obtain	produce
	4	16	that type	one type
	4	17	in	in,
	4	17	hydrolysis	hydrolysis,
	4	17	also obtained	obtained
	4	24	Cause	Take
	4	25	Method	Method to separate
	5	4	[+] gossypol or [-] gossypol	Optically active gossypol that was obtained
	5	7	can	(delete)
	5	7	outside	(delete)
		8	also	(delete)
	5	14	detailed	specific
	6	4		
	6	5		

(4) Name of document	Page	Line	Before correction	After correction
	6	7		
	7	7	C_2H_5OH	CH_3OH
	8	9 fb	Propanol	Glycerol
	9	6	this invention	this invention,
		6	regarding	relying on
		7	values	between values
		8	degree	between degrees
		8~9	results of studies of stability, this invention can be … respectively	stability, can
	16	9	mol	mol)
	10	3	etc., single solvents	etc.,
		4	or above	and above
	14	5 fb	propanol	glycerol
		4 fb	gossypol.	gossypol
	16	9 fb	[ ]	[-]
		9 fb	[M]	$[M^+]$
	16	3 fb	[+] gossypol condensed	17.5 g of [+] gossypol
		2 fb	, 17.5 g	(delete)
	19	10	reaction	reaction solution
		12	$[\alpha]^{20o}$	$[\alpha]_D^{20o}$
		14	CH_3 CH_3],	

Note: fb = from bottom

(4) Name of document	Page	Line	Before correction	After correction
	19	6 fb	N -CH-	N | -CH-
	20	2	by	through
		4	by	with the assistance of
		19	converted to [+] gossypol	converted to 1 : 1 [+] gossypol
		20	1 : 1	(delete)
	20	24	contains [+] gossypol	contains close to a 1 : 1 ratio of [+] gossypol
		25	close to 1 : 1	(delete)
	22	5	[ ]	[-]
		7	close to	ratio close to
		9	[	[-]
		10	decomposition agent	decomposition agent.
		11	optically active amine.	optically active amine
		17	remove solvent	remove solvent,
	24	1		 purchased on the market
	24	3~4	bought	
		7	extracted, dried, after which	extracted and dried, after which
Claims	3	4	propanol	glycerol
		6	propanol	glycerol
	4	4	described therein	(delete)
		5 fb	single type	in the mixture described above
		1 fb	formic acid, acetic acid	formic acid or acetic acid
		2	at least one type	at least one type of solution obtained
		3	chloroethane, and benzene	chloroethane and benzene

Note: Fb = from bottom

Optically active cotton phenol prepn. - by hydrolysis of condensate of cotton phenol and optically active amine and purification NoAbstract
Patent Assignee: MEDICINE RES INST
Inventors: HUANG L; SI Y; ZHENG D

Patent Family

Patent Number	Kind	Date	Application Number	Kind	Date	Week	Type
CN 1033795	A	19890712	CN 87105990	A	19871226	199022	B

Priority Applications (Number Kind Date): CN 87105990 A (19871226)